PCT

W[illegible]NTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :		(11) International Publication Number:	WO 00/16760
A61K 31/00	A2	(43) International Publication Date:	30 March 2000 (30.03.00)

(21) International Application Number: PCT/JP99/05152

(22) International Filing Date: 20 September 1999 (20.09.99)

(30) Priority Data:
PP 6088 23 September 1998 (23.09.98) AT

(71) Applicant (*for all designated States except US*): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): KOHNO, Yutaka [JP/JP]; 3-12-1-508, Aoba, Shimamoto-cho, Mishima-gun, Osaka 618-0015 (JP). TENDA, Yoshiyuki [JP/JP]; 3-20-11-B-1, Namiki, Tsukuba-shi, Ibaraki 305-0044 (JP). NAKAZATO, Shoko [JP/JP]; 4-20-214, Kumano-cho, Nishinomiya-shi, Hyogo 663-8103 (JP).

(74) Agent: TABUSHI, Eiji; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaki-shi, Osaka 532-8514 (JP).

(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NEW USE OF PROSTAGLANDIN E_2 ANTAGONISTS

(57) Abstract

Prostaglandin E_2 receptor blockers, particularly EP_4 receptor blocker, have diuretic activity with a various characteristics such as a lower kaluretic activity relative to natriuretic effect, a larger phosphorus excretion, or the like. Therefore, they are useful for preparation of medicament indicated treating or preventing various edema, hypertension, premenstrual tension, urinary calculus, oliguria, hyperphosphaturia, or the like.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

DESCRIPTION

NEW USE OF PROSTAGLANDIN E_2 ANTAGONISTS

Technical Field

This invention relates to a new use of prostaglandin E_2 receptor blockers.

Disclosure of Invention

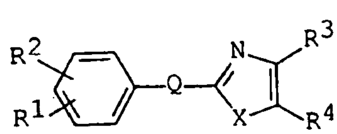
This invention relates to a new use of prostaglandin E_2 (hereinafter described as PGE_2) receptor blockers (in other words, PGE_2 antagonists), particularly EP4 receptor blocker.

In more detail, this invention relates to a new use of PGE_2 receptor blockers, particularly EP4 receptor blocker, for the manufacture of medicaments having a diuretic activity.

Accordingly, this invention provides the new use of PGE_2 receptor blockers (in other words, PGE_2 antagonists), particularly EP4 receptor blocker, for the manufacture of medicaments having a diuretic activity.

Further, this invention provides an agent and a pharmaceutical composition having a diuretic activity with a various characteristics such as a lower kaluretic activity relative to natriuretic effect, a larger phosphorus excretion, or the like.

The present invention concerns the new use of PGE_2 receptor blockers (in other words, PGE_2 antagonists), particularly EP4 receptor blocker, such as the azole compounds represented by the following formula (I) :



(I)

wherein R^1 is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; hydroxy; halo(lower)alkylsulfonyloxy; lower alkoxy optionally substituted with hydroxy or carbamoyl; aryl substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,

R^2 is hydrogen or lower alkyl,

R^3 is aryl optionally substituted with halogen,

R^4 is aryl optionally substituted with halogen,

Q is $-A^1-\bigcirc_{A^2}-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene, $\bigcirc_{A^2}$ is cyclo(C_5-C_9)alkene, cyclo(C_3-C_9)alkane, bicyclo(C_6-C_9)alkene or bicyclo(C_5-C_9)alkane, and $-A^3-$ is a single bond or lower alkylene], and

X is O, NH or S.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. Furthermore certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

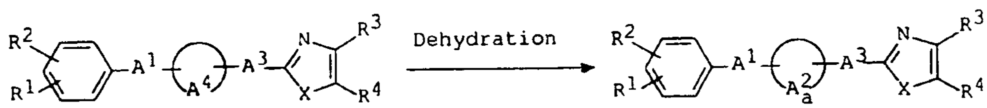
The compound of the formula (I) and its salt can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are

radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies, and any form of the crystal of the compound (I).

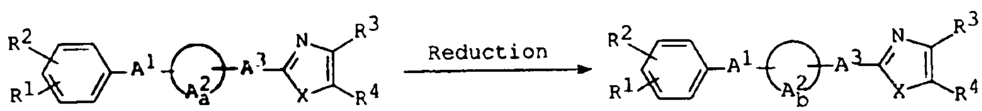
According to the present invention, the azole compounds (I) or its salt can be prepared by the processes which are illustrated in the following scheme.

Process 1



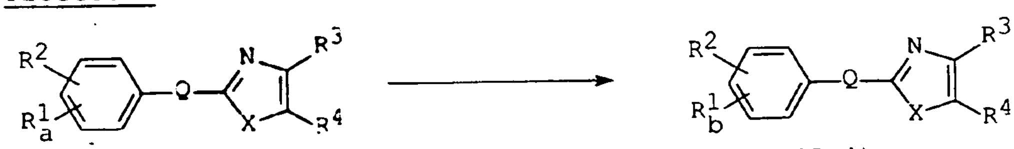
(II-1) or its salt → (I-1) or its salt

Process 2



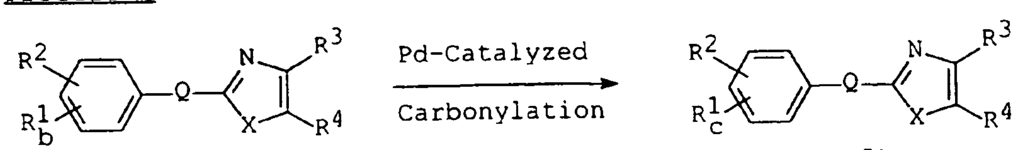
(I-1) or its salt → (I-2) or its salt

Process 3



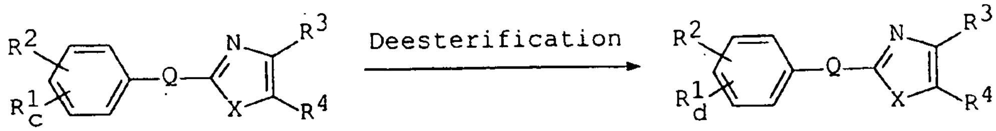
(I-3) or its salt → (I-4) or its salt

Process 4



(I-4) or its salt → (I-5) or its salt

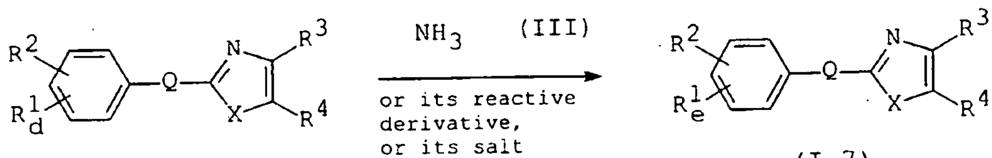
Process 5



(I-5) or its salt

(I-6) or its salt

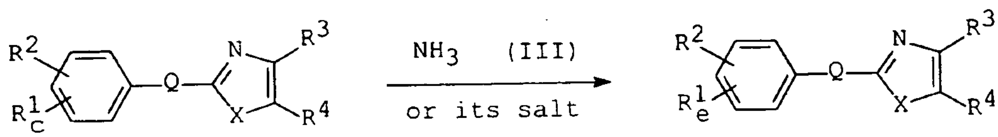
Process 6



(I-6) or its reactive derivative at carboxy group, or its salt

(I-7) or its salt

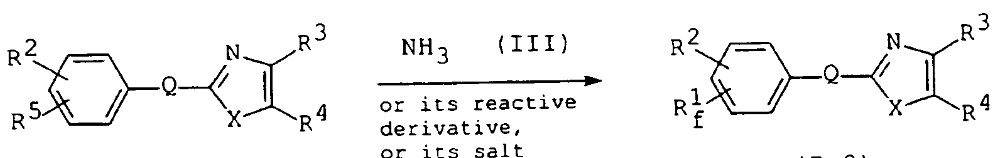
Process 7



(I-5) or its salt

(I-7) or its salt

Process 8



(II-2) or its reactive derivative at carboxy group, or its salt

(I-8) or its salt

wherein R^1, R^2, R^3, R^4, $-A^1-$, A^2, $-A^3-$, Q and X are each as defined above,

R^1_a is lower alkoxy,

R^1_b is halo(lower)alkylsulfonyloxy,

R^1_c is protected carboxy,

R^1_d is carboxy,

R^1_e is carbamoyl,

R^1_f is lower alkoxy substituted with carbamoyl,

R^5 is lower alkoxy substituted with carboxy or protected carboxy,

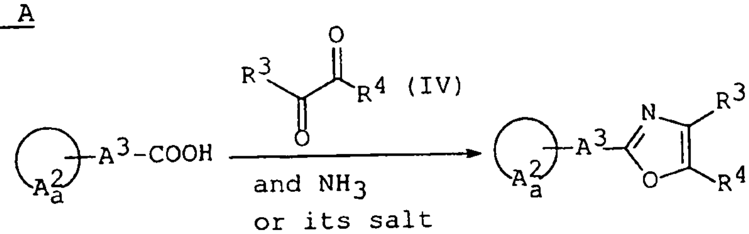
A^2_a is cyclo(C_5-C_9)alkene or bicyclo(C_6-C_9)alkene,

A^2_b is cyclo(C_5-C_9)alkane or bicyclo(C_6-C_9)alkane, and

A^4 is cyclo(C_5-C_9)alkane or bicyclo(C_6-C_9)alkane, each of which is substituted with hydroxy.

The starting compounds (II-1) and (II-2) or their salts can be prepared according to a similar method described in WO 95/17393 or the following process.

<u>Process A</u>

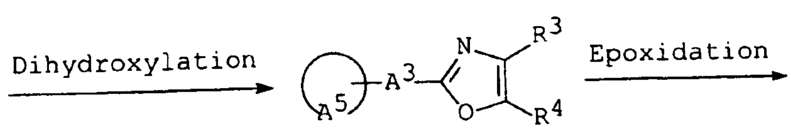


(V)

or its reactive derivative at carboxy group, or its salt

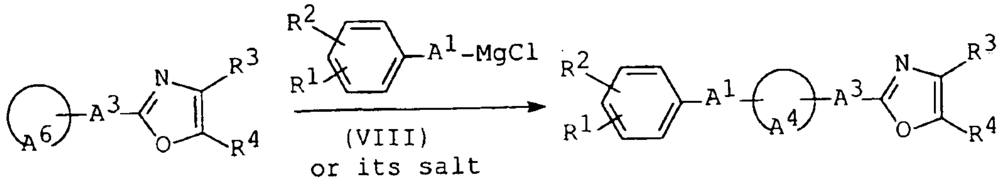
(VI)

or its salt



(VII)

or its salt



(VIII) or its salt

(IX) or its salt

(II-1) or its salt

wherein R^1, R^2, R^3, R^4, $-A^1-$, (A^2_a), $-A^3-$, (A^4) and X are each as defined above,

R^5 is hydrogen or lower alkyl,

R^6 is hydrogen or lower alkyl,

(A^5) is cyclo(C_5-C_9)alkane or bicyclo(C_6-C_9)alkane, each of which has two hydroxy groups at adjacent carbon atoms, and

(A^6) is cyclo(C_5-C_9)alkane or bicyclo(C_6-C_9)alkane, each of which has epoxy group at adjacent carbon atoms.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" and lower alkyl moiety in the term "halo(lower)alkylsulfonyl" and "lower alkylsulfonyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, t-pentyl, hexyl or the like, preferably one having 1 to 4 carbon atom(s).

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene and

hexamethylene, preferably one having 1 to 3 carbon atom(s), more preferably methylene.

Suitable "cyclo(C_3-C_9)alkane" may include cyclopropane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, or the like preferably one having 5 to 7 carbon atoms.

Suitable "cyclo(C_5-C_9)alkene" may include cyclopentene, cyclohexene, cycloheptene, cyclooctene, or the like, preferably one having 5 to 7 carbon atoms.

Suitable "bicyclo(C_5-C_9)alkane" may include bicycloheptane (e.g., bicyclo[2.2.1]heptane, etc.), bicyclooctene (e.g., bicyclo[3.2.1]octane, etc.), or the like.

Suitable "bicyclo(C_6-C_9)alkene" may include bicycloheptene (e.g., bicyclo[2.2.1]hept-2-ene, etc.), bicyclooctene (e.g., bicyclo[3.2.1]oct-2-ene, etc.), or the like.

Suitable "aryl" may include phenyl, lower alkylphenyl (e.g., tolyl, ethylphenyl, propylphenyl, etc.), naphthyl or the like.

Suitable "heterocyclic group" may include one containing at least one hetero atom selected from nitrogen, sulfur and oxygen atom, and may include saturated or unsaturated, monocyclic or polycyclic group, and preferable one may be heterocyclic group such as 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), or the like, more preferably tetrazolyl.

Suitable "lower alkoxy" may include methoxy, ethoxy propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy, or the like preferably methoxy.

Suitable "protected carboxy" may include esterified carboxy or the like.

Suitable example of the ester moiety of an esterified carboxy may be the ones such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl [e.g., acetoxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, etc.], halo(lower)alkyl (e.g., 2-iodoethyl, 2,2,2-trichloroethyl, etc.); lower alkenyl (e.g., vinyl, allyl, etc.); lower alkynyl (e.g., ethynyl, propynyl, etc.); ar(lower)alkyl which may have at least one suitable substituent(s) (e.g., benzyl, 4-methoxybenzyl, 4-nitrobenzyl, phenethyl, trityl, etc.); aryl which may have at least one suitable substituent(s) (e.g., phenyl, tolyl, 4-chlorophenyl, tert-butylphenyl, xylyl, mesityl, cumenyl, etc.); phthalidyl; or the like.

Suitable "halo" group in the term of "halo(lower)alkylsulfonyl" may include fluoro, chloro, bromo, iodo, or the like.

Suitable "halo(lower)alkylsulfonyloxy" may include trifluoromethanesulfonyloxy, or the like.

Preferred embodiments of the azole compounds (I) are as follows :

R^1 is lower alkyl substituted with carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; lower alkoxy substituted with carbamoyl; aryl substituted with carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with lower alkylsulfonyl (more preferably lower alkyl substituted with carboxy; carboxy; carbamoyl; tetrazolyl; lower alkoxy substituted with carbamoyl; aryl substituted with carboxy or carbamoyl),

R^2 is hydrogen or lower alkyl,

Q is $-A^1-\underset{A^2}{\bigcirc}-A^3-$ [in which $-A^1-$ is a single bond or

lower alkylene (more preferably methylene), A^2 is cyclo(C_5-C_9)alkene, cyclo(C_3-C_9)alkane or bicyclo(C_6-C_9)alkene, bicyclo(C_5-C_9)alkane (more preferably cyclo(C_5-C_7)alkene, cyclo(C_5-C_7)alkane, bicyclo[2.2.1]heptane or bicyclo[2.2.1]heptane), and $-A^3-$ is a single bond or lower alkylene (more preferably single bond)], and

X is O.

The processes for preparing the object and starting compounds of the present invention are explained in detail in the following.

<u>Process 1</u>

The compound (I-1) or its salt can be prepared by subjecting the compound (II-1) or its salt to dehydrating reaction.

Suitable dehydrating reagent to be used in this reaction is, for example, an organic acid, such as tolensulfonic acid (e.g., p-toluenesulfonic acid, etc.) and so on, and an inorganic acid such as hydrochlolic acd, sulfuric acid and so on.

This reaction is usually carried out in a solvent such as toluene, acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

<u>Process 2</u>

The compound (I-2) or its salt can be prepared by subjecting the compound (I-1) or its salt to reduction.

The present reduction is carried out by chemical reduction, catalytic reduction, or the like.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g., tin, zinc, iron, etc.] or metallic compound [e.g., chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.], or the like.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g., platinum, platinum black, platinum oxide, etc.], palladium catalyst [e.g., palladium black, palladium oxide, palladium on carbon, etc.], nickel catalyst [e.g., reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g., reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g., reduced iron, Raney iron, etc.], copper catalyst [e.g., reduced copper, Raney copper, Ullman copper, etc.] or the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g., methanol, ethanol, propanol, etc.], N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent and other conventional solvent such as diethyl ether, methylene chloride, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 3

The compound (I-4) or its salt can be prepared from the compound (I-3) or its salt by subjecting to (i) the cleavage of ether bond of lower alkoxy group followed by (ii) halo-

(lower)alkylsulfonylation reaction.

(i) Cleavage of ether bond

The cleavage of ether bond is carried out in the presence of an acid including the Lewis acid (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, borontribromide, etc.), tri(lower)alkylsilyl iodide, (e.g., trimethylsilyl iodide, etc.) or any other reagent ordinary employed in the field of organic synthesis.

This reaction is usually carried out in a solvent such as toluene, acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) Halo(lower)alkylsulfonylation

Suitable reagent to be used in the halo(lower)alkylsulfonylation is, for example, halo(lower)alkylsulfonyl chloride, halo(lower)alkylsulfonic anhydride (e.g., trifluoromethanesulfonic anhydride, etc.) or the like. This reaction is preferably carried out in the presence of base.

Suitable base may include the inorganic base such as alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g., magnesium carbonate, calcium carbonate, etc.) or the like, and the organic base such as tri(lower)alkylamino (e.g., trimethylamine, diisopropylethylamine, etc.), pyridine or the like.

This reaction is usually carried out in a solvent such as toluene, acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform or any other solvent which does not adversely

affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 4

The compound (I-5) or its salt can be prepared by reacting the compound (I-4) or its salt with carbon monoxide in the presence of catalytic amount of Palladium-catalyst and base.

Suitable Palladium-catalyst may be Palladium(II) acetate, Palladium(II) chloride, or the like.

Suitable base may include the inorganic base such as alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g., calcium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g., magnesium carbonate, calcium carbonate, etc.) or the like, and the organic base such as tri(lower)alkylamino (e.g., trimethylamine, diisopropylethylamine, etc.), pyridine or the like.

This reaction can be preferably carried out in the presence of a ligand, such as tri(lower)alkylphosphin (e.g., trimethylphosphine, triethylphosphine, etc.), triarylphosphine (e.g., triphenylphosphine, etc.), bis(diarylphosphino)alkane (e.g., 1,3-bis(diphenylphosphino)-propane, or the like.

This reaction is usually carried out in a solvent such as toluene, acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, dimethylsulfoxide, methylene chloride, ethylene chloride, chloroform or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 5

The compound (I-6) or its salt can be prepared by subjecting the compound (I-5) or its salt to deesterification.

Suitable method of this reaction may include conventional one such as hydrolysis, reduction or the like.

(i) For Hydrolysis :

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g., sodium, potassium, etc.], the hydroxide or carbonate or bicarbonate thereof, or the like.

Suitable acid may include an organic acid [e.g., formic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The deesterification using Lewis acid such as trihaloacetic acid [e.g., trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g., anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g., methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, 1,2-dimethoxyethane, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) For reduction :

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical

reduction are a combination of a metal (e.g., tin, zinc, iron, etc.) or metallic compound (e.g., chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g., reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g., reduced iron, Raney iron, etc.), copper catalysts (e.g., reduced copper, Raney copper, Ullman copper, etc.) or the like. The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, ethyl acetate, N,N-dimethylformamide, tetrahydrofuran, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 6

The compound (I-7) or its salt can be prepared by reacting the compound (I-6) or its reactive derivative at the carboxy group, or its salt, with the compound (III) or its reactive derivative, or its salt.

Suitable reactive derivative of the compound (III) may include Schiff's base type imino or its tautomeric enamine

type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silylating reagent such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide, or the like.

Suitable reactive derivative of the compound (I-6) may include an acid chloride, an acid anhydride, an activated amide, an activated ester, or the like.

Suitable acid anhydride may be a symmetric anhydride or a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfuric acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, chlorobenzoic acid, fluorobenzoic acid, nitrobenzoic acid, etc.), or the like.

Suitable activated amide may be imidazolylamide, 4-substituted imidazolylamide, dimethylpyrazolylamide, triazolylamide, tetrazolylamide, or the like.

Suitable activated ester may be dimethyliminomethyl $[(CH_3)_2\overset{+}{N}=CH-]$ ester, vinyl ester, propargyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, methanesulfonylphenyl ester, phenyl thioester, p-nitrophenyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, 8-quinolyl thioester, an activated ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2H-pyridone, N-hydroxysuccinimido, N-hydroxybenzotriazole, N-hydroxyphthalimide, etc.), or the like.

These reactive derivatives can optionally be selected

from them according to the kind of compound (I-6) to be used.

When the compound (I-6) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of condensing agent.

Suitable condensing agent may include a carbodiimide (e.g., N,N'-dicyclohexylcarbodiimido, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimido, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimido or its hydrochloride) diphenylphosphinic azido, diphenylphosphinic chloride, diethylphosphoryl cyanide, bis(2-oxo-3-oxazolidinyl)-phosphinic chloride, N,N'-carbonyldiimidazole, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, cyanuric chloride, or the like.

The reaction may be also carried out in the presence of organic or inorganic base such as alkali metal carbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, or the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 7

The compound (I-7) or its salt can be prepared by reacting the compound (I-5) or its salt with the compound (III) or its salt.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, methylene dichloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other

organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 8

The compound (I-8) or its salt can be prepared by reacting the compound (II-2) or its reactive derivative at the carboxy group, or its salt, with the compound (II I) or its reactive derivative, or its salt.

This reaction can be carried out in a similar manner to that of Process 6 or Process 7, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 6 and Process 7.

Process A

The compound (II-1) or (II-2), or its salt, can be prepared from the compound (V) or its salt according to the methods disclosed in the Preparation 1 to 7 or similar manners thereto.

Suitable salts of the object compound (I) and the compounds (II) to (IX) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

PGE_2 is known as one of the metabolites in an arachidonate cascade. And it is also known that it has various activities such as pain inducing activity, inflammatory activity, uterine contractile activity, a promoting effect on digestive peristalsis, an awaking activity, a suppressive effect on gastric acid secretion, hypotensive activity, blood platelet inhibition activity, bone-resorbing activity, angiogenic activity, or the like.

PGE_2-sensitive receptors have been sub-divided into four subtypes, EP1, EP2, EP3 and EP4, and these receptors have a wide distribution in various tissues. The effects associated with EP1 and EP3 receptors may be considered as excitatory, and are believed to be mediated by stimulation of phosphatidylinositol turnover or inhibition of adenyl cyclase activity, with resulting decrease in intracellular levels of cyclic AMP. In contrast, the effects associated with EP2 and EP4 receptors may be considered as inhibitory, and are believed to be associated with a stimulation of adenyl cyclase and an increase in levels of intracellular cyclic AMP. Especially, EP4 receptor may be considered to be associated with smooth muscle relaxation, anti-inflammatory or pro-inflammatory activities, lymphocyte differentiation, antiallergic activities, mesangial cell relaxation or proliferation, gastric or enteric mucus secretion, or the like.

The inventors of this invention have surprisingly found that the PGE_2 receptor blocker (in other words, PGE_2 antagonist), particularly EP4 receptor blocker, are useful for the preparation of a drug with a diuretic action.

<u>Best Mode for Carrying Out the Invention</u>

In order to show the diuretic activity of the PGE_2 receptor blocker (in other words, PGE_2 antagonist), such as the Test Compound (I), pharmacological data of the

representative compounds thereof are shown in the following.

Diuretic Activity of PGE_2 Receptor Blocker

[Test Compound]

Sodium (s)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate

[Test Method]

Prior to experiment, seven weeks female Sprague-Dawly rats were housed under standard condition for one week, and on the last day the rats were housed without food. On the day of experiment, the rats were weighted and divided into the group of five. After oral administration of the test compound and the distillation water (20 ml/kg), the rats were placed in metabolic cages and three hours urine were collected for the urinalysis.

Urinalysis: Urine volume; creatinine; sodium, potassium and phosphorus concentration in urine were measured.

[Test Results]

Table 1

	Control (0.5% MC)	Test Compound (10 mg/kg)
Urine Volume (mg/ml)	19.9±1.1	39.1±0.9**
Creatinine Clearance (L/3h/kg)	51.1±14.3	73.3±5.3
Sodium Excretion (mEq/3h/kg)	0.16±0.05	3.30±0.24**

sodium/potassium ratio in urine	0.50±0.12	4.39±0.42**
Phosphorus Excretion (mg/3h/kg)	6.4±2.4	20.3±2.0**

** : p<0.01 v.s. Control

As shown in the Table 1, the Test compound, which was selected as a representative of PGE_2 receptor blocker (in other words, PGE_2 antagonist), apparently increase sodium, potassium and phosphorus excretion. However, it showed a lower kaluretic activity relative to the potent natruretic activity. It also showed the potent phosphorus excretion activity. Therefore, PGE_2 receptor blocker (in other words, PGE_2 antagonist), especially EP4 receptor blocker, may be useful for manufacture of medicament having diuretic activity especially for hyperphosphaturia.

Effects on Renal Plasma Flow and Glomerular Filtaration Rate

[Test Compound]

Sodium (s)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate

[Test Method]

The effects on renal plasma flow (RPF) and glomerular filtration rate (GFR) were examined in anesthetized female rats by mesureament of p-nitrohippuric acid (PAH) clearance and inuline clearance, respectively. Priming doses of PAH (4 mg/rat) and inuline (20 mg/rat) were given i.v., followed by sustained infusion of PAH (0.2 %) and inuline (1 %) in physiological saline at 2 ml/rat/hr. Following equilibration period, test compound (1) was given at i.v. dose of 3.2

mg/kg.

[Test Results]

Table 2

(1) Urine Volume (ml/20 min/kg, mean ± S.E.)

	Control	Test Compound (3.2 mg/kg)
pre.	1.12 ± 0.39	0.87 ± 0.19
0- 20 min.	1.27 ± 0.35	1.01 ± 0.32
20- 40 min.	0.95 ± 0.20	1.05 ± 0.31
40- 60 min.	0.82 ± 0.15	1.79 ± 0.62
60- 80 min.	0.69 ± 0.07	2.08 ± 0.81
80-100 min.	0.72 ± 0.06	2.04 ± 0.72
100-120 min.	0.68 ± 0.05	1.95 ± 0.74

(2) PAH Clearance (ml/min/kg, mean ± S.E.)

	Control	Test Compound (3.2 mg/kg)
pre.	17.4 ± 1.9	18.3 ± 2.2
0- 20 min.	18.3 ± 2.3	21.6 ± 3.0
20- 40 min.	13.7 ± 1.4	19.9 ± 1.5
40- 60 min.	13.7 ± 1.1	27.7 ± 2.1
60- 80 min.	13.2 ± 1.4	21.3 ± 3.5
80-100 min.	15.2 ± 1.9	22.7 ± 5.3
100-120 min.	14.7 ± 2.6	18.4 ± 3.1

(3) Inuline Clearance (ml/min/kg, mean ± S.E.)

	Control	Test Compound (3.2 mg/kg)
pre.	4.69 ± 0.56	5.75 ± 0.93
0- 20 min.	6.12 ± 0.78	6.85 ± 2.23

20- 40 min.	4.43 ± 0.60	5.95 ± 0.75
40- 60 min.	4.45 ± 0.47	7.76 ± 1.63
60- 80 min.	4.44 ± 0.55	6.20 ± 1.74
80-100 min.	4.95 ± 0.84	5.51 ± 0.99
100-120 min.	4.75 ± 0.54	5.08 ± 0.89

As shown in Table 2, the Test Compound, which are representative of PGE_2 receptor blocker (in other words, PGE_2 antagonist), significantly increased urine volume at an i.v. dose of 3.2 mg/kg. Significant increases or tendency to increase were observed in RPF and GFR after the dosing, respectably.

Usual diuretics are liable to decrease RPF in patients suffering from renal failure. On the other hand, the Test compound increase RPF although it showed relative strong diuretic activity. Therefore, it must be safely given in such patients and there is a possibility that PGE_2 receptor blocker (in other words, PGE_2 antagonist), especially EP4 receptor blocker are used for the treating or preventing acute or clonic renal failure.

Binding assay using expression of prostanoide receptor subtype

[I] Test Compound :

(1) (S)-2-(4,5-Diphenyloxazol-2-yl)-1-(3-methoxybenzyl)-2-cyclopentene

(2) Sodium (S)-4-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid

(3) (S)-{3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}phenoxy}actamide

[II] Test Method :

The membrane fraction was prepared using COS-7 cells transfected prostanoide receptor subtype (human EP4). The Standard assay mixture contained membrane fraction, $[^3H]$-PGE_2 in final volume of 0.25 ml was incubated for 1 hour at 30°C. The reaction was terminated by that the mixture was rapidly filtered through a glass filter (GF/B). Then the filter was washed by 4 ml of ice-cold buffer at two times. The radioactivity associated with the filter was measured by liquid scintillation counting.

In the experiment for competition of specific $[^3H]$-PGE_2 was added at a concentration of 10 μM. The following buffer was used in all reactions.

Buffer: 20mM Mes (pH 6.0), 1mM EDTA, 10mM $MgCl_2$

The inhibition (%) of each compound at a concentration of 10μM was shown in Table.

[III] Test Result :

Test Compound	Inhibition(%)
(1) (10μM)	>80
(2) (10μM)	>80
(3) (10μM)	>80

Through the finding of this activity, PGE_2 receptor blockers (in other words, PGE_2 antagonists), particularly EP4 receptor blocker, can be used for the preparation of medicament having diuretic activity, which are useful for the preparation of drugs indicated treating or preventing various edema (e.g., cardiac edema, cerebral edema, etc.), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or

the like.

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form (e.g., tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, solution, emulsion, suspension etc.), which contains the object compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation.

The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g., sucrose, starch, mannit, sorbit, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agent (e.g., cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g., starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch, sodium glycol-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g., magnesium stearate, talc, sodium laurylsulfate, etc.), flavoring agent (e.g., citric acid, mentol, glycine, orange powders, etc.), preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (e.g., citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g., methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent (e.g., water), base wax (e.g., cacao butter, polyethyleneglycol, white petrolatum, etc.).

The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 50 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight, conditions of the patient or the administering method.

The patents, patent applications and publications cited herein are incorporated by referance.

Abbreviations used in this application are as follows :

THF	:	Tetrahydrofuran
EtOAc	:	Ethyl acetate
Et_2O	:	Diethyl ether
DMF	:	N,N-Dimethylformamide
EtOH	:	Ethyl alcohol
MeOH	:	Methyl alcohol
AcOH	:	Acetic acid
nBuli	:	n-Butyllithium
MsCl	:	Methanesulfonyl chloride
pTsOH	:	p-Toluenesulfonic acid
$AcONH_4$	:	Ammonium acetate
DMAP	:	Dimethylaminopyridine
Pd/C	:	Palladium on carbone
$Pd(OH)_2/C$	:	Palladium hydroxide on carbone

The following Preparations and Examples are given only for the purpose of illustrating the present invention in more detail.

Preparation 1

To a solution of 1-cyclohexene-1-carboxylic acid (100 g) in CH_2Cl_2 (800 ml) was added $SOCl_2$ (117 ml) at room temperature. After being stirred for 4 hours, the solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 (1 ℓ) and benzoin (170 g) and triethylamine (166 ml), and dimethylaminopyridine (10 g) were added to the solution at 0°C under N_2. After being stirred for 4 hours at room temperature, the solvent was evaporated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with 1N-HCl solution, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated in vacuo. The obtained compound and $AcONH_4$ (200 g) were dissolved in acetic acid (1500 ml) and the mixture was stirred for 4 hours at 100°C. After the solvent was removed, the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, sat. $NaHCO_3$ and brine. The dried solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel to give 1-(4,5-diphenyloxazol-2-yl)-1-cyclohexene (171 g).

NMR ($CDCl_3$, δ) : 1.6-1.9 (4H, m), 2.2-2.4 (2H, m), 2.5-2.7 (2H, m), 6.90 (1H, m), 7.2-7.8 (10H, m)

Mass (m/z) : 302$(M+H)^+$

Preparation 2

A solution of AD-*mix*-α® (30 g) in a mixture of t-BuOH (600 ml) and water (600 ml) was stirred for 1 hour, and then methanesulfonamide (9.3 g) and 1-(4,5-diphenyloxazol-2-yl)-1-cyclohexene added to the solution at room temperature. After being stirred for 20 hours at the same temperature, sodium sulfite (60 g) was added, and the mixture was stirred for 30 minutes. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1N-HCl solution, sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by chromatography on silica

gel to afford (1R,2S)-1,2-dihydroxy-1-(4,5-diphenyloxazol-2-yl)cyclohexane (30 g).

IR (neat) : 3400, 3200, 1460 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-1.9 (7H, m), 2.2-2.4 (1H, m), 3.34 (1H, s), 3.70 (1H, br s), 4.1-4.4 (1H, m), 7.2-7.8 (10H, m)

Mass (m/z) : 365 $(M+H)^+$

Preparation 3

The following compound was obtained according to a similar manner to that of Preparation 2.

(1) (1S,2R)-1,2-Dihydroxy-1-(4,5-diphenyloxazol-2-yl)-cyclohexane

IR (neat) : 3400, 3200, 1460 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-1.9 (7H, m), 2.2-2.4 (1H, m), 3.34 (1H, s), 3.70 (1H, br s), 4.1-4.4 (1H, m), 7.2-7.8 (10H, m)

Mass (m/z) : 365 $(M+H)^+$

Preparation 4

To a solution of (1R,2S)-1,2-dihydroxy-1-(4,5-diphenyloxazol-2-yl)cyclohexane (18 g) in CH_2Cl_2 (200 ml) were added orthoacetic acid trimethyl ester (9.7 ml) and p-toluenesulfonic acid (20 mg) at room temperature under N_2. After being stirred for 30 minutes, the solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 (200 ml) and acetylbromide (5.8 ml) was added to the solution at 0°C under N_2. After being stirred for 2 hours at room temperature, the solvent was evaporated in vacuo, the residue was diluted with MeOH (200 ml), and K_2CO_3 (12 g) was added to the solution at room temperature. The mixture was stirred for 2 hours at the same temperature and partitioned between ethyl acetate and water. The organic layer was washed with 1N-HCl, water, sat. $NaHCO_3$ and brine. The dried solvent was

evaporated in vacuo and the residue was purified by chromatography on silica gel to give (1R,2S)-1-(4,5-diphenyloxazol-2-yl)-1,2-epoxycyclohexane (14.1 g).

NMR ($CDCl_3$, δ) : 1.2-1.8 (4H, m), 1.9-2.2 (2H, m), 2.2-2.4 (1H, m), 2.6-2.8 (1H, m), 3.83 (1H, m), 7.2-7.6 (10H, m)

Mass (m/z) : 318 $(M+H)^+$

Preparation 5

The following compound was obtained according to a similar manner to that of Preparation 4.

(1S,2R)-1-(4,5-Diphenyloxazol-2-yl)-1,2-epoxycyclohexane

NMR ($CDCl_3$, δ) : 1.2-1.8 (4H, m), 1.9-2.2 (2H, m), 2.2-2.4 (1H, m), 2.6-2.8 (1H, m), 3.83 (1H, m), 7.2-7.6 (10H, m)

Mass (m/z) : 318 $(M+H)^+$

Preparation 6

To a solution of (1R,2S)-1-(4,5-diphenyloxazol-2-yl)-1,2-epoxycyclohexane (20 g) and CuBr (3.0 g) in tetrahydrofuran (400 ml) was dropwise added a solution of 3-methoxybenzylmagnesium chloride [prepared from 3-methoxybenzylchloride (50 g) and Mg (9.2 g)] in tetrahydrofuran (500 ml) at -78°C under N_2. The mixture was stirred for 2 hours at the room temperature and partitioned between ethyl acetate and water. The organic layer was washed with 1N-HCl, water, sat. $NaHCO_3$ and brine. The dried solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel to give (1R,2S)-1-(4,5-diphenyloxazol-2-yl)-1-hydroxy-2-(3-methoxybenzyl)cyclohexane (29.2 g).

IR (Nujol): 3400, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.4 (9H, m), 3.07 (1H, d, J=10Hz), 3.52 (1H, m), 3.74 (3H, s), 6.7-6.9 (4H, m), 7.15 (1H, t, J=8Hz), 7.2-7.8 (10H, m)

Mass (m/z) : 440 $(M+H)^+$

Preparation 7

The following compound was obtained according to a similar manner to that of Preparation 6.

(1S,2R)-1-(4,5-Diphenyloxazol-2-yl)-1-hydroxy-2-(3-methoxybenzyl)cyclohexane

Preparation 8

To a solution of diisopropylamine (1.44 ml) in THF (8 ml) was added n-BuLi (1.56M solution in hexane, 70 ml) at -60°C. The mixture was warmed to 0°C, stirred for 10 minutes, and recooled to -60°C. To the mixture was added cyclohexanone (0.98 g) in THF (5 ml). After stirring for 1 hour, 3-methoxy-2-methylbenzaldehyde (1.5 g) was added and the mixture was stirred for 1.5 hours at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution, warmed to room temperature, extracted with EtOAc. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc 4:1 to 2:1) to give 2-[hydroxy-(3-methoxy-2-methylphenyl)methyl]cyclohexanone (1.86 g) as an oil.

IR (neat): 3504, 2941, 2862, 1699, 1585, 1468, 1257 cm^{-1}
Mass (m/z) : 231 $(H+H-H_2O)^+$

Preparation 9

The following compounds described in (1) to (4) were obtained according to a similar manner to that of Preparation 8.

(1) 2-[Hydroxy-(3-methoxy-4-methylphenyl)methyl]-cyclohexanone

IR (neat) : 3502, 2939, 2862, 1699, 1612, 1585, 1508, 1466, 1452, 1412, 1255 cm^{-1}

Mass (m/z) : 231 $(M+H-H_2O)^+$

(2) 2-[Hydroxy-(3-methoxy-5-methylphenyl)methyl]-cyclohexanone

IR (neat) : 3508, 2839, 2862, 1699, 1597, 1464, 1325, 1292 cm^{-1}

Mass (m/z) : 231 $(M+H-H_2O)^+$

(3) 2-[Hydroxy-(5-methoxy-2-methylphenyl)methyl]-cyclohexanone

IR (neat) : 3508, 2939, 2862, 1697, 1610, 1581, 1500, 1450, 1300, 1248 cm^{-1}

Mass (m/z) : 231 $(M+H-H_2O)^+$

(4) 2-[Hydroxy-(2-methoxyphenyl)methyl]cyclohexanone

NMR ($CDCl_3$, δ) : 1.20-2.90 (9H, m), 3.73-3.90 (3H, m), 5.23-5.70 (1H, m), 6.80-7.52 (4H, m)

Mass (m/z) : 217 $(M+H-H_2O)^+$

Preparation 10

To a solution of 2-[hydroxy-(3-methoxy-2-methylphenyl)-methyl]cyclohexanone (1.85 g) in THF (20 ml) was added conc. HCl (0.5 ml) at 5°C and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with EtOAc, washed with saturated sodium hydrogen carbonate, water, and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was dissolved in MeOH (30 ml) and 10% Pd/C (wet) (400 mg) was added. The mixture was stirred under hydrogen atmosphere at room temperature for 2 hours. The catalyst was removed by filtration and the filtrate was evaporated. The residue was pufified by silica gel column chromatography (hexane-EtOAc 12:1 to 8:1) to give 2-(3-methoxy-2-methylbenzyl)cyclohexanone (980.6 mg) as an oil.

IR (neat): 2935, 2860, 1709, 1583, 1468, 1257, 1109 cm^{-1}.

NMR ($CDCl_3$, δ) : 1.20-2.58 (10H, m), 2.13 (3H, s), 3.22-3.34 (1H, m), 3.81 (3H, s), 6.69-6.77 (2H, m), 7.08 (1H, dd, J=7.8, 7.8Hz)

Preparation 11

The following compounds described in (1) to (3) were obtained according to a similar manner to that of Preparation 10.

(1) 2-(3-Methoxy-4-methylbenzyl)cyclohexanone

IR (neat) : 2937, 2860, 1711, 1612, 1583, 1510, 1450, 1414, 1257 cm^{-1}

NMR ($CDCl_3$, δ) : 1.23-2.62 (10H, m), 2.17 (3H, s), 3.20 (1H, dd, J=13.5, 4.4Hz), 3.81 (3H, s), 6.60-6.67 (2H, m), 7.02 (1H, d, J=7.4Hz)

(2) 2-(3-Methoxy-5-methylbenzyl)cyclohexanone

IR (neat) : 2935, 2860, 1711, 1610, 1595, 1462, 1296, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 1.22-2.63 (10H, m), 2.30 (3H, s), 3.18 (1H, dd, J=13.7, 4.4Hz), 3.77 (3H, s), 6.48-6.60 (3H, m)

Mass (m/z) : 233 $(M+H)^+$

(3) 2-(5-Methoxy-2-methylbenzyl)cyclohexanone

IR (neat) : 2935, 2862, 1709, 1610, 1579, 1502, 1448, 1309, 1288, 1254 cm^{-1}

NMR ($CDCl_3$, δ) : 1.25-2.60 (10H, m), 2.20 (3H, s), 3.22 (1H, dd, J=13.5, 3.8Hz), 3.77 (3H, s), 6.60-6.78 (2H, m), 7.00-7.10 (1H, m)

Preparation 12

A mixture of 2-[hydroxy-(2-methoxyphenyl)methyl]-cyclohexanone (3.71 g), 10% Pd/C (wet) (1.0 g), and 20%

$Pd(OH)_2/C$ (180 mg) in MeOH-EtOAc (2:1, 150 ml) was stirred under hydrogen atmosphere at room temperature for 28 hours. The catalyst was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel column chromatography (hexane-EtOAc 7:1) to give 2-(2-methoxybenzyl)cyclohexanone (2.65 g) as an oil.

IR (neat) : 2935, 2860, 1709, 1601, 1587, 1495, 1464, 1244 cm^{-1}

NMR ($CDCl_3$, δ) : 1.22-2.74 (10H, m), 3.22 (1H, dd, J=13.4, 4.6Hz), 3.79 (3H, s), 6.76-6.92 (2H, m), 7.05-7.23 (2H, m)

Mass (m/z) : 219 $(M+H)^+$

Preparation 13

To a mixture of (2-oxocyclohex-1-yl)acetic acid (5.6 g), benzoin (7.4 g), 4-dimethylaminopyridine (0.42 g) and dichloromethane (60 ml), 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (8.7 g) was added in ice-water bath. After the reaction mixture was raised to room temperature, N,N-dimethylformamide (10 ml) was added to dissolve benzoin and stirred overnight. After usual workup, 1,2-diphenyl-2-oxoethyl (2-oxocyclohex-1-yl)acetate (15.5 g) was obtained as a crude solid.

Preparation 14

A mixture of ammonium acetate (6.3 g), acetic acid (30 ml) and 1,2-diphenyl-2-oxoethyl (2-oxocyclohex-1-yl)acetate (15.0 g) was heated under reflux for 2.5 hours. After used workup, the crude product was purified by column chromatography (silica gel 100 g, eluent; hexane:ethyl acetate = 20:1 then 9:1 then 6:1) to give 2-[(4,5-diphenyl-oxazol-2-yl)methyl]cyclohexanone as an amorphous solid.

IR (film) : 2935, 1714, 1572, 1502, 1446, 1313, 1220, 1130, 1059, 962, 764, 696 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.06 (4H, m), 2.10-2.57 (4H, m),

2.70 (1H, dd, J=8.2, 15.7Hz), 2.98-3.28 (1H, m), 3.41 (1H, dd, J=7.1, 21.2Hz), 7.30-7.41 (6H, m), 7.55-7.65 (4H, m)

Mass (m/z) : 332 $(M+H)^+$, 222

Example 1

A mixture of (1R,2S)-1-(4,5-diphenyloxazol-2-yl)-1-hydroxy-2-(3-methoxybenzyl)cyclohexane (28 g) and p-toluene-sulfonic acid (2.5 g) in toluene (300 ml) was stirred for 4 hours under reflux. The solution was washed with water, sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford (S)-2-(4,5-diphenyloxazol-2-yl)-1-(3-methoxybenzyl)-2-cyclohexene (16 g).

NMR ($CDCl_3$, δ) : 1.4-1.9 (4H, m), 2.1-2.4 (2H, m), 2.53 (1H, dd, J=10.2, 12.8Hz), 3.1-3.3 (1H, m), 3.31 (1H, dd, J=3.2, 12.8Hz), 3.77 (3H, s), 6.80 (1H, 8Hz), 6.9-7.0 (3H, m), 7.20 (1H, t, J=8Hz), 7.2-7.8 (10H, m)

Mass (m/z) : 422 $(M+H)^+$

Example 2

The following compound was obtained according to a similar manner to that of Example 1.

(R)-2-(4,5-Diphenyloxazol-2-yl)-1-(3-methoxybenzyl)-2-cyclohexene

NMR ($CDCl_3$, δ) : 1.4-1.9 (4H, m), 2.1-2.4 (2H, m), 2.53 (1H, dd, J=10.2, 12.8Hz), 3.1-3.3 (1H, m), 3.31 (1H, dd, J=3.2, 12.8Hz), 3.77 (3H, s), 6.80 (1H, 8Hz), 6.9-7.0 (3H, m), 7.20 (1H, t, J=8Hz), 7.2-7.8 (10H, m)

Mass (m/z) : 422 $(M+H)^+$

Example 3

To a solution of (S)-2-(4,5-diphenyloxazol-2-yl)-1-(3-methoxybenzyl)-2-cyclohexene (8.5 g) in dichloromethane (100 ml) was added BBr_3 (50 ml, 1M solution in dichloromethane) at 0°C. After being stirred for 2 hours, the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate, and the mixture was washed with water and brine. The dried solvent was evaporated in vacuo and dissolved in dichloromethane (50 ml). To the solution were added trifluoromethanesulfonic acid anhydride (5.0 ml) and 2,6-lutidine (6.2 ml) -78°C. After being stirred for 2 hours, the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate, and the mixture was washed with water, sat. $NaHCO_3$ and brine. The dried solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel to give (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}phenyl trifluoromethanesulfonate (9.1 g).

IR (Nujol) : 1600, 1520, 1480 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (4H, m), 2.2-2.4 (2H, m), 2.60 (1H, dd, J=10.4, 13.2Hz), 3.0-3.2 (1H, m), 3.35 (1H, dd, J=4.0, 13.2Hz), 6.9 (1H, m), 7.1-7.8 (14H, m)

Mass (m/z) : 540 $(M+H)^+$

Example 4

To a dichloromethane solution (30 ml) of 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}phenol (3.06 g), triethylamine (1.5 ml) and DMAP (a catalytic amount), was added trifluoroacetic anhydride (1.5 ml) for 5 minutes at -60 °C and overnight at room temperature. The solvent was evaporated in vacuo and residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with brine. After dried over $MgSO_4$, the solution was evaporated in vacuo. The residue was purified by silica gel chromatography to afford 3-{[2-(4,5-diphenyloxazol-2-yl)-2-

cyclopenten-1-yl]methyl}pheny trifluoromethanesulfonate (3.18 g).

NMR ($CDCl_3$, δ) : 1.68-1.92 (1H, m), 2.00-2.20 (1H, m), 2.32-2.48 (2H, m), 2.75 (1H, dd, J=13.5, 9.0Hz), 3.46 (1H, dd, J=3.9, 13.5Hz), 3.54 (1H, m), 6.69 (1H, m), 7.08-7.16 (2H, m), 7.26-7.43 (8H, m), 7.60-7.72 (4H, m)

Mass (m/z) : 526 $(M+H)^+$

Example 5

The following compounds were obtained according to a similar manner to that of Example 3.

(1) (R)-3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}phenyl trifluoromethanesulfonate

(2) (S)-3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclopenten-1-yl]-methyl}phenyl trifluoromethanesulfonate

IR (Nujol) : 1600, 1580 cm^{-1}

NMR ($CDCl_3$, δ) : 1.6-2.2 (2H, m), 2.4 (2H, m), 2.75 (1H, dd, J=9.0, 13.4Hz), 3.44 (1H, dd, J=4.0, 13.4Hz), 3.56 (1H, m), 6.70 (1H, m), 7.0-7.8 (14H, m)

Mass (m/z) : 526 $(M+H)^+$

Example 6

The following compound was obtained according to a similar manner to that of Example 4.

4-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}phenyl trifluoromethanesulfonate

NMR ($CDCl_3$, δ) : 1.4-2.0 (4H, m), 2.6-2.8 (1H, m), 3.0-3.2 (1H, m), 6.86 (1H, m), 7.0-7.5 (14H, m)

Example 7

To a solution of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-

cyclohexen-1-yl]methyl}phenyl trifluoromethanesulfonate (7 g) in a mixture of methanol (30 ml) and dimethylformamide (40 ml) were added 1,3-bis(diphenylphosphino)propane (1.1 mg), palladium acetate (0.58 mg), and triethylamine (5.4 ml). After being stirred for 5 hours at 80°C under CO atmosphere, the mixture was partitioned between ethyl acetate and water and the organic layer was washed with 1N-HCl, sat. $NaHCO_3$, and brine. The dried solvent was evaporated in vacuo and the obtained solid was washed with ether to afford methyl (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-benzoate (4.2 g).

IR (Nujol): 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (4H, m), 2.1-2.4 (2H, m), 2.62 (1H, dd, J=10.0, 13.0Hz), 3.16 (1H, m), 3.33 (1H, dd, J=3.0, 13.0Hz), 3.88 (3H, s), 6.92 (1H, t, J=4.0Hz), 7.3-7.8 (12H, m), 7.85 (1H, d, J=8Hz), 8.00 (1H, s)

Mass (m/z) : 450 $(M+H)^+$

Example 8

The following compounds were obtained according to a similar manner to that of Example 7.

(1) Methyl (R)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate

IR (Nujol): 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (4H, m), 2.1-2.4 (2H, m), 2.62 (1H, dd, J=10.0, 13.0Hz), 3.16 (1H, m), 3.33 (1H, dd, J=3.0, 13.0Hz), 3.88 (3H, s), 6.92 (1H, t, J=4.0Hz), 7.3-7.8 (12H, m), 7.85 (1H, d, J=8Hz), 8.00 (1H, s)

Mass (m/z) : 450 $(M+H)^+$

(2) Methyl 4-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate

IR (Nujol): 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (4H, m), 2.2-2.4 (2H, m), 2.63 (1H, dd, J=10.2, 13.0Hz), 3.20 (1H, m), 3.39 (1H, dd, J=3.4, 13.0Hz), 3.89 (3H, s), 6.92 (1H, m), 7.2-7.8 (12H, m), 7.96 (2H, d, J=8Hz)

Mass (m/z) : 450 $(M+H)^+$

(3) Ethyl (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}benzoate

IR (Nujol) : 1720 cm^{-1}

Mass (m/z) : 450 $(M+H)^+$

Example 9

To a solution of methyl (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate (0.3 g) in a mixture of ethanol (8 ml) and tetrahydrofuran (5 ml) was added 1N-NaOH solution (3.5 ml). After being stirred for 24 hours at the same temperature, the solvent was removed. The residue was partitioned between ethyl acetate and 1N-HCl and the organic layer was washed with brine. The dried solvent was evaporated in vacuo and the obtained solid was washed with a mixture hexane and ether to afford (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid(0.28 g).

IR (Nujol) : 1700 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-1.9 (4H, m), 2.2-2.4 (2H, m), 2.65 (1H, dd, J=10.0, 13.0Hz), 3.2 (1H, m), 3.35 (1H, dd, J=3.0, 13.0Hz), 6.93 (1H, t, J=3.8Hz), 7.2-7.8 (12H, m), 7.93 (1H, d, J=8Hz), 8.10 (1H, s)

Mass (m/z) : 436 $(M+H)^+$

Example 10

The following compounds were obtained according to a similar manner to that of Example 9.

(1) (R)-3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-

methyl}benzoic acid
IR (Nujol) : 1700 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.9 (4H, m), 2.2-2.4 (2H, m), 2.65 (1H, dd, J=10.0, 13.0Hz), 3.2 (1H, m), 3.35 (1H, dd, J=3.0, 13.0Hz), 6.93 (1H, t, J=3.8Hz), 7.2-7.8 (12H, m), 7.93 (1H, d, J=8Hz), 8.10 (1H, s)
Mass (m/z) : 436 $(M+H)^+$

(2) 4-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}benzoic acid
IR (Nujol) : 1690 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.9 (4H, m), 2.2-2.4 (2H, m), 2.6-2.8 (1H, m), 3.2 (1H, m), 3.40 (1H, dd, J=3.2, 13.2Hz), 6.93 (1H, m), 7.2-7.8 (12H, m), 8.03 (2H, d, J=8Hz)
Mass (m/z) : 436 $(M+H)^+$

(3) (S)-3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}benzoic acid
IR (Nujol) : 1680 cm^{-1}
NMR ($CDCl_3$) : 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.38-2.52 (2H, m), 2.74 (1H, dd, J=12.7, 9.1Hz), 3.46 (1H, dd, J=12.7, 4.2Hz), 3.60 (1H, m), 6.72 (1H, m), 7.2-7.7 (12H, m), 7.9-8.0 (2H, m).
Mass (m/z) : 422 $(M+H)^+$

(4) 3-{[(1S,2S)-2-(4,5-Diphenyloxazol-2-yl)-1-cyclopentyl]-methyl}benzoic acid
IR (Nujol) : 1680 cm^{-1}
NMR (CDCl3, δ) : 1.4-2.4 (6H, m), 2.4-2.8 (3H, m), 3.52 (1H, m), 7.2-7.4 (8H, m), 7.5-7.7 (4H, m), 7.8-8.0 (2H, m)
Mass (m/z) : 424 $(M+H)^+$

(5) 3-{[(1S,2R)-2-(4,5-Diphenyloxazol-2-yl)-1-cyclopentyl]-

methyl}benzoic acid

Mass (m/z) : 424 $(M+H)^+$

IR (Nujol) : 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.5 (6H, m), 2.5-3.1 (4H, m), 7.2-7.8 (12H, m), 7.82 (1H, d, J=8Hz), 7.93 (1H, S)

(6) 3-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclopenten-1-yl]-methyl}benzoic acid

IR (Nujol) : 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 1.7-2.0 (2H, m), 2.4-2.6 (2H, m), 2.9-3.1 (2H, m), 4.21 (2H, s), 7.2-7.7 (10H, m), 7.9-8.1 (4H, m)

Mass (m/z) : 422 $(M+H)^+$

Example 11

A mixture of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid (0.1 g) and 10% Pd/C (0.1 g) in methanol (20 ml) was stirred under H_2 for 8 hours. The catalyst was filtered off and filtrate was evaporated in vacuo to give 3-{[(1S)-2-(4,5-diphenyloxazol-2-yl)-1-cyclohexyl]methyl}benzoic acid (0.1 g).

IR (neat) : 3400, 1690 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-2.5 (9H, m), 2.6-3.0 (2H, m), 3.25 (1H, m), 7.2-8.1 (14H, m)

Mass (m/z) : 438 $(M+H)^+$

Example 12

The following compounds were obtained from ethyl (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]-methyl}benzoate according to a similar manner to that of Example 11.

(1) Ethyl 3-{[(1S,2S)-2-(4,5-diphenyloxazol-2-yl)-1-cyclopentyl]methyl}benzoate

(2) Ethyl 3-{[(1S,2R)-2-(4,5-diphenyloxazol-2-yl)-1-cyclopentyl]methyl}benzoate

Example 13

To a solution of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid (0.3 g) in a tetrahydrofuran (10 ml) were added isobutyl chloroformate (0.15 ml) and triethylamine (0.2 ml) at 0°C under N_2. After being stirred for 30 minutes, NH_3 (5 ml, 4M solution in methanol) was added to the mixture. After being stirred for 30 minutes, the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and 1N-NaOH and the organic layer was washed with brine. The dried solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel to give and the obtained residue was purified by chromatography on silica gel to give (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-benzamide (0.03 g).

IR (Nujol) : 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-1.0 (4H, m), 2.2-2.4 (2H, m), 2.65 (1H, dd, J=9.8, 13.0Hz), 3.15 (1H, m), 3.20 (1H, dd, J=4.0, 13.0Hz), 5.5 (1H, br s), 6.1 (1H, br s), 6.92 (1H, m), 7.2-7.9 (13H, m)

Mass (m/z) : 435 $(M+H)^+$

Example 14

The following compounds were obtained according to a similar manner to that of Example 13.

(1) 3-{[(1S,2S)-2-(4,5-Diphenyloxazol-2-yl)-1-cyclopentyl]-methyl}benzamide

IR (Nujol) : 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.4 (6H, m), 2.4-2.8 (3H, m), 3.48 (1H, m), 5.6 (1H, br s), 6.09 (1H, br s), 7.2-7.7 (14H, m)

Mass (m/z) : 423 $(M+H)^+$

(2) 3-{[(1S,2R)-2-(4,5-Diphenyloxazol-2-yl)-1-cyclopentyl]-methyl}benzamide

IR (Nujol) : 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.5 (6H, m), 2.6-3.0 (4H, m), 5.4 (1H, br s), 6.0 (1H, br s), 7.2-7.7 (14H, m)

Mass (m/z) : 423 $(M+H)^+$

(3) 3-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclopenten-1-yl]-methyl}benzamide

IR (Nujol) : 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.8-2.0 (2H, m), 2.4-2.6 (2H, m), 2.9-3.1 (2H, m), 4.19 (2H, s), 4.67 (1H, br s), 5.96 (1H, br s), 7.2-7.8 (14H, m)

Mass (m/z) : 421 $(M+H)^+$

Example 15

To a solution of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid (3 g) in a methanol (30 ml) was added 1N-NaOH solution (6.9 ml). After being stirred for 5 minutes, the solvent was removed in vacuo to give sodium (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate (3 g).

NMR ($DMSO-d_6$) : 1.4-2.0 (4H, m), 2.2-2.4 (2H, m), 3.0-3.1 (1H, m), 6.91 (1H, m), 7.0-7.8 (12H, m), 7.83 (1H, s)

Example 16

To a solution of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid (0.2 g) in a tetrahydrofuran (10 ml) were added isobutyl chloroformate (0.15 ml) and triethylamine (0.2 ml) at 0°C under N_2. After being stirred for 30 minutes, NH_3 (5 ml, 4M solution in methanol) was added to the mixture. After being stirred for

30 minutes, the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and 1N-NaOH and the organic layer was washed with brine. The dried solvent was evaporated in vacuo. The residue and 10 % Pd/C (0.2 g) in methanol (20 ml) was stirred under H_2 for 8 hours. The catalyst was filtered off and filtrate was evaporated in vacuo. The residue was purified by chromatography on silica gel to give and the obtained residue was purified by chromatography on silica gel to give 3-{[(1S)-2-(4,5-diphenyloxazol-2-yl)-1-cyclohexyl]methyl}benzamide (0.11 g).

IR (neat) : 3300, 3200, 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-2.4 (9H, m), 2.5-2.8 (2H, m), 3.2 (1H, m), 5.5 (1H, br s), 6.0 (1H, br s), 7.2-7.8 (14H, m)

Mass (m/z) : 437 $(M+H)^+$

Example 17

A dimethylformamide (8 ml) - MeOH (4 ml) solution of 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}-phenyl trifluoromethanesulfonate (2.24 g), Palladium(II) acetate (64 mg), 1,3-bis(diphenylphosphino)propane (106 mg) and triethylamine (1.2 ml) was saturated with CO gas. The solution was stirred for 14 hours at 70°C under CO atmosphere. The solvent was evaporated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was washed with 1N hydrochloric acid, water and brine. After dried over $MgSO_4$, the organic solvent was evaporated in vacuo. The residue was purified by silica gel chromatography to afford methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}benzoate (1.17 g).

IR (neat) : 1710, 1630 cm^{-1}

NMR ($CDCl_3$, δ) : 1.65-1.97 (1H, m), 1.97-2.19 (1H, m), 2.39-2.50 (2H, m), 2.71 (1H, dd, J=13.4, 9.2Hz), 3.46 (1H, dd, J=13.4, 4.1Hz), 3.78 (1H, m), 3.88 (3H, s), 6.70 (1H, m), 7.29-7.46 (8H, m), 7.59-7.72

(4H, m), 7.83-7.93 (2H, m)

Example 18

To a methanol solution (7 ml) of methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}benzoate (1.15 g) was added 1N aqueous sodium hydroxide solution (4 ml). The solution was stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with brine. After dried over $MgSO_4$, the organic solvent was evaporated in vacuo to afford 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}-benzoic acid (1.02 g).

IR (Nujol) : 1680 cm^{-1}

NMR ($CDCl_3$, δ) : 1.72-1.92 (1H, m), 2.00-2.20 (1H, m), 2.38-2.52 (2H, m), 2.74 (1H, dd, J=12.7, 9.1Hz), 3.46 (1H, dd, J=12.7, 4.2Hz), 3.60 (1H, m), 6.72 (1H, m), 7.26-7.72 (12H, m), 7.90-8.01 (2H, m)

Mass (m/z) : 422 $(M+H)^+$

Example 19

To a tetrahydrofuran solution (10 ml) of 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}benzoic acid (0.30 g) and triethylamine (0.15 ml) was added ethyl chloroformate (0.15 ml) at 0°C. The solution was stirred for 30 minutes at the same temperature. Then aqueous ammonia (10 ml) was added to the solution. After stirred for 6 hours at 0°C, the solution was partitioned between ethyl acetate and water. The organic layer was washed with water, 1N hydrochloric acid, water and brine. After dried over $MgSO_4$, the solvent was evaporated in vacuo to afford 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}benzamide (0.24 g).

IR (Nujol) : 3800, 3160, 1640, 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 1.72-2.20 (2H, m), 2.38-2.54 (2H, m),

2.72 (1H, dd, J=13.5, 9.1Hz), 3.43 (1H, dd, J=13,5, 4.0Hz), 3.60 (1H, m), 6.71 (1H, m), 7.34-7.52 (9H, m), 7.57-7.70 (7H, m)

Mass (m/z) : 421 $(M+H)^+$, 403 $(M-NH_3)^+$

Example 20

3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclopenten-1-yl]-methyl}benzamide (75 mg) was hydrogenated over 5% Pd/C (3 mg) in methanol (20 ml) at room temperature at 3 atm for 7 hours. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was triturated with a mixture of ether and n-hexane to afford 3-{[2-(4,5-diphenyloxazol-2-yl)-1-cyclopentyl]methyl}benzamide (54 mg).

IR (KBr) : 3334, 3199, 3059, 2954, 2869, 1662 cm^{-1}

NMR ($DMSO-d_6$, δ) : 1.20-3.12 (9H, m), 3.48 (1H, m), 7.15-8.00 (16H, m)

Mass (m/z) : 423 $(M+H)^+$, 405 $(M-NH_3)^+$

Example 21

To a solution of ethyl (S)-(3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}phenoxy)acetate (0.5 g) in tetrahydrofuran (5 ml) was added NH_3 (5 ml, 4N methanol solution). After being stirred for 24 hours, the solvent was removed. The residue was purified by chromatography on silica gel to give (S)-(3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}phenoxy)acetamide (220 mg).

IR (Nujol) : 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (4H, m), 2.2-2.4 (2H, m), 2.56 (1H, dd, J=9.8, 12.8Hz), 3.20 (1H, m), 3.32 (1H, dd, J=4.0, 12.8Hz), 4.46 (2H, s), 5.8 (1H, br s), 6.5 (1H, br s), 6.8-7.8 (14H, m)

Mass (m/z) : 465 $(M+H)^+$

Example 22

To a solution of 2-(4,5-diphenyloxazol-2-yl)-3-(3-methoxybenzyl)bicyclo[2.2.1]hept-2-ene (3.4 g) in dichloromethane (35 ml) was added BBr_3 (17 ml, 1M solution in dichloromethane) at 0°C. After being stirred for 2 hours, the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate, and the mixture was washed with water and brine. The dried solvent was evaporated in vacuo and dissolved in dichloromethane (20 ml). To the solution were added trifluoromethanesulfonic anhydride (0.8 ml) and 2,6-lutidine (1.1 ml) -78°C. After being stirred for 2 hours, the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate, and the mixture was washed with water, sat. $NaHCO_3$ and brine. The dried solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel to give a Tf-compound [3-{[3-(4,5-diphenyloxazol-2-yl)bicyclo[2.2.1]hept-2-en-2-yl]methyl}phenyl trifluoromethansulfonate] (1.6 g).

To a solution of the Tf-compound (1.6 g) in a mixture of methanol (10 ml) and DMF (20 ml) were added 1,3-bis(diphenylphosphino)propane (480 mg), palladium acetate (260 mg), and triethylamine (1.2 ml). After being stirred for 5 hours at 80°C under carbone monooxide atmosphere, the mixture was partitioned between ethyl acetate and water and the organic layer was washed with 1N-HCl, sat. $NaHCO_3$, and brine. The dried solvent was evaporated in vacuo and the obtained solid was washed with ether to afford methyl 3-{[3-(4,5-diphenyloxazol-2-yl)bicyclo[2.2.1]hept-2-en-2-yl]-methyl}benzoate (1.0 g).

IR (Nujol) : 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.0-2.0 (6H, m), 2.85 (1H, br s), 3.62 (1H, br s), 3.86 (1H, d, J=14Hz), 3.89 (3H, s), 4.40 (1H, d, J=14Hz), 7.2-8.0 (14H, m)

Mass (m/z) : 462 $(M+H)^+$

Example 23

The following compound was obtained according to a similar manner to that of Example 22.

Methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohepten-1-yl]methyl}benzoate

IR (Nujol) : 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (6H, m), 2.4-2.6 (2H, m), 2.91 (1H, dd, J=10.0, 14.0Hz), 3.09 (1H, dd, J=6.6, 14Hz), 3.81 (3H, s), 7.08 (1H, t, J=8.0Hz), 7.2-7.8 (12H, m), 7.80 (1H, d, J=8Hz), 8.00 (1H, s)

Mass (m/z) : 464 $(M+H)^+$

Example 24

To a solution of methyl 3-{[3-(4,5-diphenyloxazol-2-yl)bicyclo[2.2.1]hept-2-en-2-yl]methyl}benzoate (1.0 g) in a mixture of methanol (10 ml) and THF (10 ml) was added 1N-NaOH solution (11 ml). After being stirred for 5 minutes, the solvent was removed in vacuo. The residue was dissolved in a mixture of ethyl acetate and 1N-HCl solution. The organic layer was washed with brine and dried over $MgSO_4$. The solution was evaporated in vacuo to give 3-{[3-(4,5-diphenyloxazol-2-yl)bicyclo[2.2.1]hept-2-en-2-yl]methyl}-benzoic acid (1.0 g).

IR (Nujol) : 1690 cm^{-1}

NMR ($CDCl_3$, δ) : 1.0-2.0 (6H, m), 2.86 (1H, br s), 3.68 (1H, br s), 3.86 (1H, d, J=15Hz), 4.39 (1H, d, J=14Hz), 7.2-8.2 (14H, m)

Mass (m/z) : 448 $(M+H)^+$

Example 25

The following compounds described in (1) to (3) were obtained in a similar manner to that of Example 24.

(1) 3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohepten-1-yl]-methyl}benzoic acid

IR (Nujol) : 1690 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (6H, m), 2.4-2.6 (2H, m), 2.94 (1H, dd, J=10.0, 14.0Hz), 3.12 (1H, dd, J=10, 14Hz), 4.11 (1H, m), 7.11 (1H, t, J=8.0Hz), 7.2-7.8 (12H, m), 7.89 (1H, d, J=8Hz), 8.10 (1H, s)

Mass (m/z) : 450 $(M+H)^+$

(2) (S)-3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}phenylacetic acid

NMR ($CDCl_3$, δ) : 1.4-1.8 (4H, m), 2.1-2.4 (2H, m), 2.5-2.8 (1H, m), 3.1-3.4 (2H, m), 6.93 (1H, m), 7.0-8.2 (14H, m)

Mass (m/z) : 450 $(M+H)^+$

(3) 3-{3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}phenyl}propionic acid sodium salt

IR (Nujol) : 1580 cm^{-1}

NMR ($DMSO-d_6$, δ) : 1.4-2.0 (4H, m), 2.1-2.5 (5H, m), 2.6-2.9 (2H, m), 2.9-3.2 (2H, m), 6.8-7.2 (4H, m), 7.2-7.8 (10H, m)

Mass (m/z) : 464 $(M+H-Na)^+$

Example 26

To a solution of 3-{[3-(4,5-diphenyloxazol-2-yl)-bicyclo[2.2.1]hept-2-en-2-yl]methyl}benzoic acid (0.46 g) in a THF (10 ml) were added isobutyl chloroformate (0.26 ml) and triethylamine (0.3 ml) at 0°C under N_2. After being stirred for 30 minutes, NH_3 (5 ml, 4M solution in methanol) was added to the mixture. After being stirred for 30 minutes, the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and 1N-NaOH and the organic layer was washed with brine. The dried solvent was evaporated in vacuo to give 3-{[3-(4,5-diphenyloxazol-2-yl)bicyclo[2.2.1]hept-2-en-2-yl]methyl}benzamide (0.2 g).

IR (neat) : 3350, 3150, 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-2.4 (6H, m), 2.86 (1H, br s), 3.61 (1H, br s), 3.82 (1H, d, J=14Hz), 4.40 (1H, d, J=14Hz), 7.2-7.8 (14H, m)

Mass (m/z) : 447 $(M+H)^+$

Example 27

The following compound was obtained in a similar manner to that of Example 26.

3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohepten-1-yl]methyl}-benzamide

IR (neat) : 3350, 3150, 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.0 (6H, m), 2.42 (2H, m), 2.91 (1H, dd, J=8.6, 13.4Hz), 3.10 (1H, dd, J=7.2, 13.4Hz), 3.78 (1H, m), 7.09 (1H, t, J=8Hz), 7.2-7.8 (14H, m)

Mass (m/z) : 449 $(M+H)^+$

Example 28

A solution of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid (0.5 g), diphenylphosphoryl azide (0.30 ml), and triethylamine (0.2 ml) in toluene (20 ml) was stirred for 1 hour under reflux. To the mixture was added benzylalcohol and stirred for 15 hours under reflux. The cooled solvent was evaporated in vacuo and the obtained residue was purified by chromatography on silica gel to afford benzyl (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}phenylcarbamate (0.4 g).

IR (Nujol) : 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-1.8 (4H, m), 2.3 (1H, m), 2.53 (1H, dd, J=9.6, 12Hz), 3.20 (1H, m), 3.28 (1H, dd, J=4.0, 12Hz), 5.19 (2H, s), 6.60 (1H, s), 6.86 (1H, m), 7.03 (1H, d, J=8Hz), 7.2-7.8 (13H, m)

Mass (m/z) : 541 $(M+H)^+$

Example 29

A mixture of 3-{[3-(4,5-diphenyloxazol-2-yl)bicyclo-[2.2.1]hept-2-en-2-yl]methyl}benzoic acid (0.3 g) and 10% Pd/C (0.1 g) in methanol (20 ml) was stirred under H_2 for 8 hours. The catalyst was filtered off and filtrate was evaporated in vacuo to give 3-{[3-(4,5-diphenyloxazol-2-yl)-bicyclo[2.2.1]hept-2-yl]methyl}benzoic acid (0.27 g).

IR (Nujol) : 1690 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-2.8 (11H, m), 3.60 (1H, m), 7.2-8.0 (14H, m)

Mass (m/z) : 450 $(M+H)^+$

Example 30

The following compounds described in (1) to (4) were obtained in a similar manner to that of Example 29.

(1) 3-{[3-(4,5-Diphenyloxazol-2-yl)bicyclo[2.2.1]hept-2-yl]methyl}benzamide

IR (Nujol) : 1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-2.8 (11H, m), 3.52 (1H, m), 7.2-7.8 (14H, m)

Mass (m/z) : 449 $(M+H)^+$

(2) 3-{[2-(4,5-Diphenyloxazol-2-yl)-1-cycloheptyl]methyl}-benzoic acid

IR (Nujol) : 1690 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-2.2 (10H, m), 2.5-3.0 (3H, m), 3.34 (1H, m), 7.2-6.0 (12H, m), 7.8-8.0 (2H, m)

Mass (m/z) : 452 $(M+H)^+$

(3) 3-{[2-(4,5-Diphenyloxazol-1-yl)-1-cycloheptyl]methyl}-benzamide

IR (Nujol) : 1640 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-2.2 (10H, m), 2.4-3.0 (3H, m), 3.28 (1H, m), 7.2-7.8 (10H, m)

Mass (m/z) : 451 $(M+H)^+$

(4) (S)-3-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclohexyl]-methyl}aniline

IR (Nujol) : 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-2.8 (11H, m), 3.22 (1H, m), 6.4-6.6 (2H, m), 7.0-7.8 (12H, m)

Mass (m/z) : 409 $(M+H)^+$

Example 31

To a solution of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-1-cyclohexyl]methyl}aniline (70 mg) in dichloromethane (10 ml) were added pyridine (1 ml) and MsCl (0.032 ml). After stirred for 2 hours at the room temperature, the mixture was partitioned between ethyl acetate and water and the organic layer was washed with 1N-HCl, sat. $NaHCO_3$, and brine. The dried solvent was evaporated in vacuo and the obtained solid was washed with ether to afford (S)-N-{3-{[2-(4,5-diphenyloxazol-2-yl)-1-cyclohexyl]methyl}phenyl}-methanesulfonamide (0.05 g).

IR (Nujol) : 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-2.8 (11H, m), 2.87 (3H, s), 3.2 (1H, m), 6.37 (1H, m), 6.9-7.8 (14H, m)

Mass (m/z) : 487 $(M+H)^+$

Example 32

To a solution 4,5-diphenyloxazole (1.2 g) in THF (20 ml) was added n-BuLi (3.7 ml, 1.6M solution in hexane) at -78°C. After stirred for 30 minutes at the same temperature, a solution of 2-(3-cyanobenzyl)hexanone (1.0 g) in THF (10 ml) was added to the mixture. After stirred for 2 hours at the same temperature, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1N-HCl, water, sat. $NaHCO_3$ and brine. The dried solvent was evaporated in vacuo and the residue was purified by

chromatography on silica gel to give alcohol compound. A mixture of the alcohol compound and p-toluenesulfonic acid (0.01 g) in toluene (30 ml) was stirred for 7 hours under reflux. The solution was washed with water, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}benzonitrile (0.86 g).

IR (Nujol) : 2200 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-1.9 (4H, m), 2.2-2.4 (2H, m), 2.59 (1H, dd, J=10.0, 13.2Hz), 3.1-3.3 (1H, m), 3.33 (1H, dd, J=3.4, 13.2Hz), 6.92 (1H, d, J=3.8Hz), 7.2-7.8 (14H, m)

Mass (m/z) : 417 $(M+H)^+$

Example 33

The following compound was obtained in a similar manner to that of Example 32.

Ethyl 3-{3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}phenyl}propionate

IR (Nujol) : 1730 cm^{-1}

NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=8Hz), 1.4-2.0 (4H, m), 2.2-2.4 (2H, m), 2.5-2.8 (3H, m), 2.8-3.0 (2H, m), 3.1-3.3 (2H, m), 4.17 (2H, q, J=8Hz),6.8-7.1 (2H, m), 7.1-7.8 (13H, m)

Mass (m/z) : 492 $(M+H)^+$

Example 34

To a solution of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}phenyl trifluoromethanesulfonate (1.17 g) in dichloromethane (100 ml) were added 5-(2-boronophenyl)-2-(triphenylmethyl)-2H-tetrazole (1.16 g), tetrakis(triphenylphosphine)palladium (600 mg), and K_2CO_3 (630 mg) in a mixture of DMF and water. After being stirred

for 8 hours at 100°C, the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel to give (S)-2-(4,5-diphenyloxazol-2-yl)-1-{3-{2-[2-(triphenylmethyl)tetrazol-5-yl]phenyl}benzyl}-2-cyclohexene (0.83 g).

IR (Nujol) : 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-1.8 (4H, m), 2.2-2.4 (3H, m), 3.0-3.2 (2H, m), 6.8-7.0 (6H, m), 7.0-8.0 (27H, m)

Example 35

To a solution of (S)-2-(4,5-diphenyloxazol-2-yl)-1-{3-{2-[2-(triphenylmethyl)tetrazol-5-yl]phenyl}benzyl}-2-cyclohexene (0.8 g) in methanol (20 ml) was added conc. HCl solution (2 ml). After being stirred for 4 hours, the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel to give (S)-2-(4,5-diphenyloxazol-2-yl)-1-{3-[2-(tetrazol-5-yl)phenyl]benzyl}-2-cyclohexene (50 mg).

IR (Nujol) : 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-1.8 (4H, m), 2.2-2.4 (2H, m), 2.6-3.2 (3H, m), 6.8-7.6 (19H, m), 8.03 (1H, d, J=8Hz)

Mass (m/z) : 536 $(M+H)^+$

Example 36

To a solution of 2-(4,5-diphenyloxazol-2-yl)-1-(3-cyanobenzyl)-2-cyclohexene (400 mg) in DMF (8 ml) were added NaN_3 (100 mg) and NH_4Cl (80 mg). After stirred for 12 hours at 120°C, the mixture was partitioned between ethyl acetate and water and the organic layer was washed with 1N-HCl and brine. The dried solvent was evaporated in vacuo and the obtained solid was washed with a mixture of ether and n-hexane to afford 2-(4,5-diphenyloxazol-2-yl)-1-{3-(1H-tetrazol-5-yl)benzyl}-2-cyclohexene (0.36 g).

NMR ($CDCl_3$, δ) : 1.3-2.0 (4H, m), 2.2-2.5 (2H, m), 2.66 (1H, dd, J=10, 14Hz), 3.1-3.3 (2H, m), 6.91 (1H, t, J=4.2Hz), 7.1-7.8 (12H, m), 7.8-8.0 (2H, m)

Mass (m/z) : 460 $(M+H)^+$

Example 37

To a solution of (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid (0.2 g) in CH_2Cl_2 (10 ml) was added $SOCl_2$ (1 ml) and stirred for 1 hour at the room temperature. After the solvent was evaporated in vacuo, the residue was dissolved in a mixture of THF and CH_3CN. To the solution were added (trimethylsilyl)diazomethane (0.34 ml) and triethylamine (0.1 ml) at 0°C. After stirred for 48 hours at the same temperature, the solvent was evaporated in vacuo, and benzylalcohol (1.8 ml) and 2,4,6-collidine (1.8 ml) were added to there. After stirred for 20 minutes at 180°C, the mixture was diluted with toluene and purified by chromatography on silica gel to afford benzyl (S)-3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}phenylacetate (0.14 g).

IR (Nujol) : 1720 cm^{-1}

NMR ($CDCl_3$, δ) : 1.4-1.8 (4H, m), 2.3-2.5 (2H, m), 2.4-2.6 (1H, m), 3.0-3.4 (2H, m), 6.92 (1H, m), 7.0-8.0 (19H, m)

Mass (m/z) : 540 $(M+H)^+$

Example 38

To a solution of 4,5-diphenyloxazole (990 mg) in THF (15 ml) was added n-BuLi (1.56M solution in hexane, 2.87 ml) at -60°C and stirred for 1 hour. To the mixture was added a solution of 2-(3-methoxy-2-methylbenzyl)cyclohexanone (945 mg) in THF (4 ml), warmed to 5°C, and stirred for 2 hours. To the reaction mixture was added 1N HCl and extracted with EtOAc. The organic layer was washed with water, saturated sodium hydrogen carbonate, water, and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was dissolved in toluene (45 ml) and p-TsOH·H_2O (79 mg) was added. The mixture was refluxed for 48 hours, cooled to room

temperature, diluted with EtOAc, washed with saturated sodium hydrogen carbonate, water, and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc 15:1 to 10:1) to give 2-[1-(3-methoxy-2-methylbenzyl)-2-cyclohexen-2-yl]-4,5-diphenyloxazole (1.19 g) as an amorphous solid.

IR (KBr) : 3057, 2933, 2862, 1643, 1583, 1537, 1462, 1444, 1255 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.40 (6H, m), 2.42 (3H, s), 2.62 (1H, dd, J=13.1, 10.8Hz), 3.10-3.28 (1H, m), 3.35 (1H, dd, J=13.1, 3.8Hz), 3.80 (3H, s), 6.70 (1H, d, J=7.9Hz), 6.82-6.95 (2H, m), 7.07 (1H, dd, J=7.9, 7.9Hz), 7.30-7.50 (6H, m), 7.58-7.77 (4H, m)

Mass (m/z) : 436 $(M+H)^+$

Example 39

The following compounds described in (1) to (4) were obtained in a similar manner to that of Example 38.

(1) 2-[1-(3-Methoxy-4-methylbenzyl)-2-cyclohexen-2-yl]-4,5-diphenyloxazole

IR (neat) : 3053, 2933, 2860, 1610, 1585, 1533, 1506, 1446, 1411, 1255 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-1.90 (4H, m), 2.17 (3H, s), 2.18-2.40 (2H, m), 2.52 (1H, dd, J=12.8, 9.9Hz), 3.06-3.30 (2H, m), 3.79 (3H, s), 6.79 (1H, d, J=7.3Hz), 6.84-6.95 (2H, m), 7.03 (1H, d, J=7.3Hz), 7.23-7.42 (6H, m), 7.55-7.75 (4H, m)

Mass (m/z) : 436 $(M+H)^+$

(2) 2-[1-(3-Methoxy-5-methylbenzyl)-2-cyclohexen-2-yl]-4,5-diphenyloxazole

IR (neat) : 3053, 2933, 2860, 1595, 1533, 1462, 1446, 1294, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-1.95 (4H, m), 2.10-2.58 (3H, m),

2.30 (3H, s), 3.08-3.27 (2H, m), 3.76 (3H, s), 6.55 (1H, s), 6.72 (1H, s), 6.77 (1H, s), 6.92 (1H, dd, J=4.0, 4.0Hz), 7.23-7.45 (6H, m), 7.58-7.78 (4H, m)

Mass (m/z) : 436 $(M+H)^+$

(3) 2-[1-(5-Methoxy-2-methylbenzyl)-2-cyclohexen-2-yl]-4,5-diphenyloxazole

IR (neat) : 3055, 2935, 2862, 1606, 1535, 1502, 1446, 1250 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-1.95 (4H, m), 2.07-2.47 (2H, m), 2.41 (3H, s), 2.60 (1H, dd, J=14.5, 12.0Hz), 3.10-3.33 (2H, m), 3.75 (3H, s), 6.65 (1H, dd, J=8.4, 2.7Hz), 6.82-6.96 (2H, m), 7.04 (1H, d, J=8.4Hz), 7.20-7.43 (6H, m), 7.53-7.76 (4H, m)

Mass (m/z) : 436 $(M+H)^+$

(4) 2-[1-(2-Methoxybenzyl)-2-cyclohexen-2-yl]-4,5-diphenyloxazole

IR (neat) : 3057, 2935, 2862, 1601, 1535, 1493, 1444, 1242 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.00 (4H, m), 2.10-2.38 (2H, m), 2.80 (1H, dd, J=12.9, 10.3Hz), 3.05-3.33 (2H, m), 3.78 (3H, s), 6.75-6.95 (3H, m), 7.07-7.43 (8H, m), 7.55-7.77 (4H, m)

Mass (m/z) : 422 $(M+H)^+$

Example 40

To a solution of 2-[1-(3-methoxy-2-methylbenzyl)-2-cyclohexen-2-yl]-4,5-diphenyloxazole (1.16 g) in CH_2Cl_2 (25 ml) was added boron tribromide (1M solution in CH_2Cl_2, 5.32 ml) at -60°C and the mixture was warmed to 5°C. After stirring for 1 hour at the same temperature, the reaction mixture was stirred for further 1 hour at room temperature. To the mixture was added water under ice-cooling, extracted with EtOAc. The organic layer was washed with water,

saturated sodium hydrogen carbonate, water, and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc 5:1) to give 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-2-methylphenol (903.8 mg) as an amorphous solid.

IR (KBr) : 3330, 3059, 2933, 2862, 1645, 1585, 1537, 1466, 1446, 1273 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35-2.40 (6H, m), 2.45 (3H, s), 2.60 (1H, dd, J=13.3, 11.1Hz), 3.07-3.25 (1H, m), 3.37 (1H, dd, J=13.3, 3.8Hz), 4.67 (1H, s), 6.62 (1H, d, J=7.9Hz), 6.80 (1H, d, J=7.9Hz), 6.85-7.02 (2H, m), 7.20-7.45 (6H, m), 7.55-7.75 (4H, m)

Mass (m/z) : 422 $(M+H)^+$

Example 41

The following compounds described in (1) to (4) were obtained in a similar manner to that of Example 40.

(1) 5-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-2-methylphenol

IR (KBr) : 3319, 3062, 2931, 2858, 1589, 1523, 1446, 1419, 1242, 1119 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-1.90 (4H, m), 2.08-2.36 (2H, m), 2.20 (3H, s), 2.47 (1H, dd, J=12.7, 9.9Hz), 3.05-3.27 (2H, m), 4.73 (1H, s), 6.70-6.83 (2H, m), 6.83-6.95 (1H, m), 7.02 (1H, d, J=7.4Hz), 7.22-7.45 (6H, m), 7.55-7.75 (4H, m)

Mass (m/z) : 422 $(M+H)^+$

(2) 3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-5-methylphenol

IR (KBr) : 3330, 3032, 2931, 2858, 1595, 1535, 1444, 1311, 1298, 1153 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-1.90 (4H, m), 2.07-2.56 (3H, m), 2.27 (3H, s), 3.06-3.26 (2H, m), 4.82 (1H, s), 6.47

(1H, s), 6.61 (1H, s), 6.74 (1H, s), 6.92 (1H, dd, J=4.0, 4.0Hz), 7.22-7.45 (6H, m), 7.55-7.77 (4H, m)

Mass (m/z) : 422 $(M+H)^+$

(3) 3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-4-methylphenol

IR (KBr) : 3356, 2935, 2862, 1606, 1587, 1535, 1502, 1444 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-1.98 (4H, m), 2.10-2.47 (2H, m), 2.40 (3H, s), 2.56 (1H, dd, J=14.3, 11.8Hz), 3.10-3.33 (2H, m), 4.75 (1H, s), 6.57 (1H, dd, J=8.3, 2.7Hz), 6.76 (1H, d, J=2.7Hz), 6.91 (1H, dd, J=3.9, 3.9Hz), 6.98 (1H, d, J=8.3Hz), 7.20-7.43 (6H, m), 7.53-7.73 (4H, m)

Mass (m/z) : 422 $(M+H)^+$

(4) 2-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}phenol

IR (KBr) : 3180, 3057, 2937, 1645, 1579, 1535, 1485, 1446, 1344, 1227 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30-2.00 (4H, m), 2.15-2.55 (3H, m), 2.82-2.98 (1H, m), 3.28-3.43 (1H, m), 6.72-7.50 (11H, m), 7.54-7.77 (4H, m)

Mass (m/z) : 408 $(M+H)^+$

Example 42

To a solution of 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-2-methylphenol (894 mg) and 2,6-lutidine (0.494 ml) in CH_2Cl_2 (18 ml) was added trifluoromethanesulfonic anhydride (0.534 ml) at 5°C and the mixture was stirred for 1 hour. The solvent was removed in vacuo and the residue was diluted with EtOAc, washed with water, 1N HCl, water, and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc 15:1) to give

3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-2-methylphenyl trifluoromethanesulfonate (960.8 mg) as an oil.

IR (neat) : 3059, 2939, 1537, 1448, 1419, 1250, 1217, 1140 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-1.95 (4H, m), 2.25-2.42 (2H, m), 2.54 (3H, s), 2.67 (1H, dd, J=13.4, 10.9Hz), 3.08-3.25 (1H, m), 3.42 (1H, dd, J=13.4, 3.6Hz), 6.88-6.95 (1H, m), 7.05-7.45 (9H, m), 7.55-7.74 (4H, m)

Mass (m/z) : 554 $(M+H)^+$

Example 43

The following compounds described in (1) to (4) were obtained in a similar manner to that of Example 42.

(1) 5-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-2-methylphenyl trifluoromethanesulfonate

IR (neat) : 3060, 2935, 2863, 1506, 1446, 1419, 1250, 1213, 1142, 1074 cm^{-1}

NMR ($CDCl_3$, δ) : 1.45-1.85 (4H, m), 2.08-2.46 (2H, m), 2.33 (3H, s), 2.56 (1H, dd, J=13.3, 10.4Hz), 3.05-3.19 (1H, m), 3.22-3.35 (1H, m), 6.87-6.97 (1H, m), 7.15-7.44 (9H, m), 7.55-7.75 (4H, m)

Mass (m/z) : 554 $(M+H)^+$

(2) 3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-5-methylphenyl trifluoromethanesulfonate

IR (neat) : 3059, 2935, 2864, 1620, 1585, 1533, 1446, 1421, 1240, 1213, 1142 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-1.90 (4H, m), 2.08-2.40 (2H, m), 2.36 (3H, s), 2.54 (1H, dd, J=13.2, 10.3Hz), 3.05-3.35 (2H, m), 6.85-6.95 (2H, m), 7.08 (1H, s), 7.19 (1H, s), 7.23-7.47 (6H, m), 7.57-7.77 (4H, m)

Mass (m/z) : 554 $(M+H)^+$

(3) 3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-

methyl}-4-methylphenyl trifluoromethanesulfonate

IR (neat) : 3055, 2937, 2866, 1535, 1491, 1446, 1423, 1250, 1213, 1142 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-1.93 (4H, m), 2.18-2.50 (2H, m), 2.51 (3H, s), 2.63 (1H, dd, J=13.3, 11.0Hz), 3.08-3.25 (1H, m), 3.35 (1H, dd, J=13.3, 3.7Hz), 6.93 (1H, dd, J=3.8, 3.8Hz), 6.99 (1H, dd, J=8.4, 2.7Hz), 7.15-7.23 (2H, m), 7.23-7.47 (6H, m), 7.55-7.77 (4H, m)

Mass (m/z) : 554 $(M+H)^+$

(4) 2-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}phenyl trifluoromethanesulfonate

IR (neat) : 3059, 2937, 2866, 1533, 1487, 1448, 1419, 1248, 1215, 1140 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.00 (4H, m), 2.10-2.50 (2H, m), 2.94 (1H, dd, J=14.5, 10.7Hz), 3.14-3.34 (2H, m), 6.87-6.98 (1H, m), 7.10-7.78 (14H, m)

Mass (m/z) : 540 $(M+H)^+$

Example 44

A mixture of 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-2-methylphenyl trifluoromethanesulfonate (955 mg), palladium(II) acetate (117 mg), 1,3-bis(diphenylphosphino)propane (214 mg), triethylamine (0.72 ml), and MeOH (6 ml) in DMF (12 ml) was purged for 30 minutes with carbon monoxide. The mixture was stirred under carbon monoxide atmosphere at 95°C for 1 hour. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with water, 1N HCl, water, saturated sodium hydrogen carbonate, water, and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc 13:1) to give methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-2-methylbenzoate (226.3 mg) as an

amorphous solid.

IR (KBr) : 3064, 2937, 2862, 1722, 1537, 1448, 1257 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.00 (4H, m), 2.10-2.50 (2H, m), 2.57-2.75 (1H, m), 2.73 (3H, s), 3.10-3.30 (1H, m), 3.43 (1H, dd, J=13.6, 4.1Hz), 3.88 (3H, s), 6.91 (1H, dd, J=3.9, 3.9Hz), 7.13 (1H, dd, J=7.6, 7.6Hz), 7.25-7.43 (7H, m), 7.55-7.75 (5H, m)

Mass (m/z) : 464 $(M+H)^+$

Example 45

The following compounds described in (1) to (4) were obtained in a similar manner to that of Example 44.

(1) Methyl 5-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-2-methylbenzoate

IR (KBr) : 3055, 2933, 2860, 1722, 1536, 1500, 1444, 1290, 1259 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-1.90 (4H, m), 2.10-2.38 (2H, m), 2.54 (3H, s), 2.58 (1H, dd, J=13.2, 10.3Hz), 3.07-3.35 (2H, m), 3.85 (3H, s), 6.88-6.97 (1H, m), 7.16 (1H, d, J=7.8Hz), 7.22-7.43 (7H, m), 7.55-7.75 (4H, m), 7.87 (1H, d, J=0.9Hz)

Mass (m/z) : 464 $(M+H)^+$

(2) Methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-5-methylbenzoate

IR (KBr) : 3059, 2933, 2860, 1720, 1604, 1537, 1444, 1309, 1219 cm^{-1}

NMR ($CDCl_3$, δ) : 1.35-1.95 (4H, m), 2.10-2.45 (2H, m), 2.35 (3H, s), 2.58 (1H, dd, J=12.7, 9.5Hz), 3.10-3.33 (2H, m), 3.87 (3H, s), 6.92 (1H, dd, J=3.9, 3.9Hz), 7.25-7.46 (7H, m), 7.58-7.77 (5H, m), 7.79 (1H, s)

Mass (m/z) : 464 $(M+H)^+$

(3) Methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-4-methylbenzoate

IR (KBr) : 3045, 2935, 2862, 1718, 1606, 1537, 1439, 1296, 1267 cm^{-1}

NMR ($CDCl_3$, δ) : 1.42-2.04 (4H, m), 2.20-2.45 (2H, m), 2.56 (3H, s), 2.67 (1H, dd, J=13.2, 10.3Hz), 3.10-3.30 (1H, m), 3.35 (1H, dd, J=13.2, 4.2Hz), 3.85 (3H, s), 6.83-6.93 (1H, m), 7.18 (1H, d, J=8.0Hz), 7.21-7.45 (6H, m), 7.54-7.78 (5H, m), 7.91 (1H, d, J=1.7Hz)

Mass (m/z) : 464 $(M+H)^+$

(4) Methyl 2-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate

IR (neat) : 3057, 2935, 2862, 1722, 1603, 1533, 1487, 1446, 1261 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.00 (4H, m), 2.10-2.50 (2H, m), 3.20-3.43 (3H, m), 3.86 (3H, s), 6.88-6.98 (1H, m), 7.10-7.80 (14H, m)

Mass (m/z) : 450 $(M+H)^+$

Example 46

A mixture of 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}phenyl trifluoromethanesulfonate (400 mg), 3-methoxycarbonylphenylboronic acid (177 mg), triethylamine (0.318 ml), and tetrakis(triphenylphosphine)palladium(0) (64 mg) in DMF (8 ml) was stirred at 100°C for 3.5 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc, washed with water, 1N HCl, water, saturated sodium hydrogen carbonate, water, and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc 10:1) to give methyl 3'-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]-methyl}biphenyl-3-carboxylate (264.6 mg) as an oil.

IR (neat) : 3057, 2949, 2843, 1724, 1603, 1441, 1308, 1252 cm^{-1}

NMR ($CDCl_3$, δ) : 1.80-2.20 (2H, m), 2.39-2.54 (2H, m), 2.75 (1H, dd, J=13.4, 9.1Hz), 3.45 (1H, dd, J=13.4, 4.3Hz), 3.52-3.72 (1H, m), 3.93 (3H, s), 6.68-6.76 (1H, m), 7.23-7.78 (16H, m), 7.95-8.05 (1H, m), 8.23-8.30 (1H, m)

Mass (m/z) : 512 $(M+H)^+$

Example 47

To a solution of methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-2-methylbenzoate (119 mg) in EtOAc (8 ml) and MeOH (10 ml) was added 10% Pd/C (wet) (60 mg) and the mixture was stirred under hydrogen atmosphere at 3 atm at room temperature for 18 hours. The catalyst was removed by filtration and the filtrate was evaporated to give methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-1-cyclohexyl]methyl}-2-methylbenzoate (115.3 mg) as an amorphous solid.

IR (KBr) : 3064, 2929, 2854, 1720, 1560, 1502, 1446, 1261 cm^{-1}

NMR ($CDCl_3$, δ) : 1.00-2.90 and 3.18-3.33 (total 12H, each m), 2.41 and 2.42 (total 3H, each s), 3.84 and 3.86 (total 3H, each s), 6.98-7.73 (13H, m)

Mass (m/z) : 466 $(M+H)^+$

Example 48

The following compounds described in (1) to (3) were obtained in a similar manner to that of Example 47.

(1) Methyl 5-{[2-(4,5-diphenyloxazol-2-yl)-1-cyclohexyl]-methyl}-2-methylbenzoate

IR (neat) : 3057, 2929, 2854, 1722, 1604, 1563, 1500, 1446, 1261, 1200 cm^{-1}

NMR ($CDCl_3$, δ) : 1.00-2.80 and 3.15-3.28 (total 12H, each m), 2.45 and 2.50 (total 3H, each s), 3.77 and

3.79 (total 3H, each s), 7.00-7.73 (13H, m)

Mass (m/z) : 466 $(M+H)^+$

(2) Methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-1-cyclohexyl]-methyl}-5-methylbenzoate

IR (neat) : 3057, 2929, 2854, 1722, 1604, 1564, 1446, 1309, 1219 cm^{-1}

NMR ($CDCl_3$, δ) : 1.05-2.80 and 3.15-3.26 (total 12H, each m), 2.21 and 2.27 (total 3H, each s), 3.79 and 3.82 (total 3H, each s), 7.10 (1H, br s), 7.20-7.73 (12H, m)

Mass (m/z) : 466 $(M+H)^+$

(3) Methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-1-cyclohexyl]-methyl}-4-methylbenzoate

IR (neat) : 3057, 2931, 2856, 1720, 1606, 1566, 1444, 1296, 1269 cm^{-1}

NMR ($CDCl_3$, δ) : 1.03-2.85 and 3.18-3.33 (total 12H, each m), 2.27 and 2.28 (total 3H, each s), 3.79 and 3.80 (total 3H, each s), 7.03-7.17 (1H, m), 7.22-7.88 (12H, m)

Mass (m/z) : 466 $(M+H)^+$

Example 49

A mixture of methyl 3'-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}biphenyl-3-carboxylate (204 mg) and 10% Pd/C (wet) (50 mg) in EtOAc (3 ml) and MeOH (3 ml) was stirred under hydrogen atmosphere at room temperature for 14 hours. The catalyst was removed by filtration and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane-EtOAc 12:1 to 6:1) to give methyl 3'-{[2-(4,5-diphenyloxazol-2-yl)-1-cyclopentyl]methyl}biphenyl-3-carboxylate (172.1 mg) as an oil.

IR (neat) : 3057, 2951, 2871, 1724, 1604, 2566, 1442,

1308, 1252 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38-2.38 (6H, m), 2.41-3.10 and 3.44-3.48 (total 4H, each m), 3.92 and 3.93 (total 3H, each s), 7.10-7.73 (16H, m), 7.92-8.02 (1H, m), 8.14-8.23 (1H, m)

Mass (m/z) : 514 $(M+H)^+$

Example 50

To a solution of methyl 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}-2-methylbenzoate (100 mg) in MeOH-1,4-dioxane (1:2, 4.5 ml) was added 1N NaOH solution (1.0 ml) and the mixture was stirred at 70°C for 1 hour. After cooling, the mixture was acidified with 1N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo to give 3-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-2-methylbenzoic acid (97.0 mg) as a solid.

IR (KBr) : 3059, 2935, 2860, 2646, 1685, 1587, 1539, 1446, 1302, 1269 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30-2.05 (4H, m), 2.05-2.50 (2H, m), 2.55-2.75 (1H, m), 2.65 (3H, s), 2.93-3.17 (1H, m), 3.18-3.45 (1H, m), 6.85-6.95 (1H, m), 7.19 (1H, dd, J=7.5, 7.5Hz), 7.30-7.70 (12H, m), 12.80 (1H, br)

Mass (m/z) : 450 $(M+H)^+$

Example 51

The following compounds described in (1) to (9) were obtained in a similar manner to that of Example 50.

(1) 3-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclohexyl]methyl}-2-methylbenzoic acid

IR (KBr) : 3059, 2929, 2854, 2642, 1689, 1560, 1446, 1240 cm^{-1}

NMR ($CDCl_3$, δ) : 1.00-2.95 and 3.20-3.33 (total 12H, each m), 2.50 (3H, s), 7.00-7.80 (13H, m)

Mass (m/z) : 452 $(M+H)^+$

(2) 5-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-2-methylbenzoic acid

IR (KBr) : 3026, 2931, 2860, 2654, 1689, 1604, 1570, 1533, 1500, 1446, 1267 cm^{-1}

NMR ($DMSO-d_6$, δ) : 1.35-1.95 (4H, m), 2.06-2.70 (3H, m), 2.47 (3H, s), 2.90-3.30 (2H, m), 6.83-6.97 (1H, m), 7.22 (1H, d, J=7.8Hz), 7.27-7.74 (11H, m), 8.00 (1H, s), 12.79 (1H, br)

Mass (m/z) : 450 $(M+H)^+$

(3) 5-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclohexyl]methyl}-2-methylbenzoic acid

IR (KBr) : 3057, 2927, 2854, 1687, 1606, 1562, 1500, 1446, 1254 cm^{-1}

NMR ($CDCl_3$, δ) : 1.00-2.87 and 3.17-3.30 (total 12H, each m), 2.52 and 2.57 (total 3H, each s), 7.03-7.90 (13H, m)

Mass (m/z) : 452 $(M+H)^+$

(4) 3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-5-methylbenzoic acid

IR (KBr) : 3049, 2933, 2860, 1682, 1603, 1529, 1446, 1309, 1244 cm^{-1}

NMR ($DMSO-d_6$, δ) : 1.30-1.98 (4H, m), 2.08-2.70 (3H, m), 2.32 (3H, s), 2.93-3.25 (2H, m), 6.85-6.95 (1H, m), 7.30-7.73 (12H, m), 7.77 (1H, s), 12.84 (1H, br)

Mass (m/z) : 450 $(M+H)^+$

(5) 3-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclohexyl]methyl}-5-methylbenzoic acid

IR (KBr) : 3059, 2927, 2854, 1687, 1604, 1560, 1446, 1308, 1240 cm^{-1}

NMR ($CDCl_3$, δ) : 1.00-2.85 and 3.18-3.32 (total 12H,

each m), 2.24 and 2.30 (total 3H, each s), 7.16 (1H, br s), 7.20-7.75 (12H, m)

Mass (m/z) : 452 $(M+H)^+$

(6) 3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl}-4-methylbenzoic acid

IR (KBr) : 3028, 2931, 2864, 1689, 1610, 1576, 1537, 1446, 1425, 1309, 1279 cm^{-1}

NMR ($DMSO-d_6$, δ) : 1.40-2.00 (4H, m), 2.10-2.43 (2H, m), 2.51 (3H, s), 2.60-2.78 (1H, m), 3.00-3.40 (2H, m), 6.88-6.97 (1H, m), 7.25 (1H, d, J=7.9Hz), 7.33-7.74 (11H, m), 7.87 (1H, s)

Mass (m/z) : 450 $(M+H)^+$

(7) 3-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclohexyl]methyl}-4-methylbenzoic acid

IR (KBr) : 3056, 2929, 2856, 1687, 1608, 1560, 1446, 1273, 1242 cm^{-1}

NMR ($CDCl_3$, δ) : 1.05-2.88 and 3.18-3.33 (total 12H, each m), 2.29 and 2.30 (total 3H, each s), 7.07-7.20 (1H, m), 7.20-7.95 (12H, m)

Mass (m/z) : 452 $(M+H)^+$

(8) 3'-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclopenten-1-yl]-methyl}biphenyl-3-carboxylic acid

IR (KBr) : 3055, 2929, 1691, 1603, 1543, 1444, 1306, 1240 cm^{-1}

NMR ($DMSO-d_6$, δ) : 1.60-2.20 (2H, m), 2.35-2.58 (2H, m), 2.65-2.83 (1H, m), 3.10-3.85 (2H, m), 6.70-6.77 (1H, m), 7.20-7.98 (17H, m), 8.18 (1H, s)

Mass (m/z) : 498 $(M+H)^+$

(9) 3'-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclopentyl]methyl}-biphenyl-3-carboxylic acid

IR (KBr) : 3055, 2952, 2870, 1691, 1603, 1560, 1444,

1306, 1240 cm^{-1}

NMR (DMSO-d_6, δ) : 1.35-2.25 (6H, m), 2.50-3.60 (4H, m), 7.11-7.58 (15H, m), 7.68-7.80 (1H, m), 7.80-7.93 (1H, m), 8.07-8.17 (1H, m)

Mass (m/z) : 500 $(M+H)^+$

Example 52

To a solution of methyl 2-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate (37 mg) in MeOH-1,4-dioxane (1:1, 3 ml) was added 1N NaOH solution (1.0 ml) at 5°C and the mixture was stirred at 80°C for 3 hours. After cooling, the mixture was acidified with 1N HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was dissolved in MeOH-1,4-dioxane (1:1, 2 ml) and 1N NaOH solution (0.0824 ml) was added thereto. The mixture was evaporated and Et_2O was added. The resulting solid was collected by filtration to give sodium 2-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate (19.9 mg).

IR (KBr) : 3421, 3057, 2929, 1603, 1579, 1558, 1442, 1406 cm^{-1}

NMR (DMSO-d_6, δ) : 1.20-2.43 (6H, m), 2.80-3.20 (2H, m), 3.55-3.73 (1H, m), 6.80-6.90 (1H, m), 6.93-7.15 (2H, m), 7.20-7.53 (8H, m), 7.55-7.70 (4H, m)

Mass (m/z) : 458 $(M+H)^+$

Example 53

To a solution of 3'-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}biphenyl-3-carboxylic acid (74 mg) and N-methylmorpholine (0.0197 ml) in THF (4 ml) was added isobutyl chloroformate (0.0232 ml) at 0°C. After stirring for 15 minutes, 28% ammonia solution (0.1 ml) was added thereto. The mixture was stirred at the same temperature for 15 minutes, then stirred at room temperature for 15 minutes.

The reaction mixture was diluted with EtOAc, washed with water, 1N HCl, water, and brine, dried over magnesium sulfate, evaporated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2-MeOH 25:1) to give 3'-{[2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl}-biphenyl-3-carboxamide (51.8 mg) as a solid.

IR (KBr) : 3375, 3182, 3060, 1647, 1587, 1523, 1444, 1406 cm^{-1}

NMR (DMSO-d_6, δ) : 1.75-2.20 (2H, m), 2.35-2.55 (2H, m), 2.74 (1H, dd, J=13.3, 9.2Hz), 3.25-3.43 (2H, m), 6.70-6.78 (1H, m), 7.20-7.70 (16H, m), 7.70-7.90 (2H, m), 8.05-8.20 (2H, m)

Mass (m/z) : 497 $(M+H)^+$

Example 54

The following compound was obtained in a similar manner to that of Example 53.

3'-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclopentyl]methyl}-biphenyl-3-carboxamide

IR (neat) : 3348, 3194, 3059, 2958, 2871, 1666, 1603, 1577, 1446, 1408, 1383 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-3.15 and 3.40-3.58 (total 10H, each m), 7.10-7.68 (16H, m), 7.70-7.80 (1H, m), 7.90-7.95 (1H, m)

Mass (m/z) : 499 $(M+H)^+$

Example 55

To a solution of 4-bromoanisole (1.00 g) in tetrahydrofuran (4 ml), n-butyllithium hexane solution (1.56M, 3.4 ml) was added at -78°C under a flow of nitrogen. After stirring for 0.5 hour, a solution of 2-[(4,5-diphenyloxazol-2-yl)methyl]cyclohexan-1-one (1.36 g) in tetrahydrofuran (3 ml) was added below -50°C to the reaction mixture and stirred for 0.5 hour. After usual workup, the

crude product was purified by column chromatography (silica gel 50 g, eluent; hexane/ethyl acetate = 9 then 4) to give 2-[(4,5-diphenyloxazol-2-yl)methyl]-1-(3-methoxyphenyl)-1-cyclohexanol (1.01 g) as a foam.

IR (film) : 3420, 2935, 1604, 1581, 1484, 1446, 1288, 1249, 1160, 1056, 1047, 964, 775, 696 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-2.0 (10H, m), 2.38-2.58 (1H, m), 2.68 (2H, d, J=6.1Hz), 3.78 (3H, s), 6.70-6.76 (1H, m), 7.08-7.45 (9H, m), 7.49-7.63 (4H, m)

Mass (m/z) : 440 $(M+H)^+$, 422

Example 56

A mixture of 2-[(4,5-diphenyloxazol-2-yl)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol (990 mg), p-toluenesulfonic acid monohydrate (22 mg) and acetic acid (5 ml) was heated at 130°C for 6 hours. After usual workup and purification by column chromatography (silica gel, 45 g, eluent; hexane/ethyl acetate = 9), 1-[(4,5-diphenyloxazol-2-yl)methyl]-2-(3-methoxyphenyl)-2-cyclohexene (551 mg) as a pasty solid.

IR (film) : 2931, 1602, 1574, 1487, 1454, 1429, 1286, 1205, 1171, 1057, 962, 764, 694 cm^{-1}

NMR ($CDCl_3$, δ) : 1.63-1.80 (2H, m), 1.80-1.92 (2H, m), 2.15-2.29 (2H, m), 2.75 (1H, dd, J=9.5, 14.9Hz), 2.93 (1H, dd, J=5.0, 14.9Hz), 3.32-3.50 (1H, m), 3.73 (3H, s), 6.00-6.04 (1H, m), 6.68-6.76 (1H, m), 6.88-6.99 (2H, m), 7.14 (1H, t, J=7.9Hz), 7.28-7.42 (6H, m), 7.48-7.62 (4H, m)

Mass (m/z) : 422 $(M+H)^+$

Example 57

The following compounds described in (1) to (2) were prepared in a similar manner to that of Example 38.

(1) A mixture of 3-(4,5-diphenyloxazol-2-yl)-1-(3-methoxybenzyl)-2-cyclohexene and 3-(4,5-diphenyloxazol-

2-yl)-1-(3-methoxybenzyl)-3-cyclohexene

IR (film) : 2929, 1601, 1585, 1487, 1448, 1261, 1153, 1061, 1043, 964, 766, 694 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-1.4 (1H, m), 1.7-2.1 (2H, m), 2.1-2.4 (2H, m), 2.50-2.92 (4H, m), 3.81 (3H, s), 6.72-6.96 (4H, m), 7.18-7.45 (7H, m), 7.54-7.72 (4H, m)

Mass (m/z) : 422 $(M+H)^+$

(2) A mixture of 3-(4,5-diphenyloxazol-2-yl)-1-(3-methoxyphenyl)-2-cyclohexene and 3-(4,5-diphenyloxazol-2-yl)-1-(3-methoxyphenyl)-3-cyclohexene

Example 58

The following compounds described in (1) to (2) were obtained in a similar manner to that of Example 22.

(1) A mixture of methyl 3-{[3-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoate and methyl 3-{[3-(4,5-diphenyloxazol-2-yl)-3-cyclohexen-1-yl]methyl}benzoate

IR (film) : 2929, 1722, 1537, 1446, 1284, 1203, 1107, 964, 764, 696 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-1.5 (1H, m), 1.7-2.4 (4H, m), 2.5-2.9 (4H), 3.91 (3H, s), 6.78 (0.4H, br s), 6.88 (0.6H, br s), 7.30-7.48 (8H, m), 7.56-7.70 (4H, m), 7.86-7.96 (2H, m)

Mass (m/z) : 450 $(M+H)^+$

(2) A mixture of methyl 3-[3-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]benzoate and methyl 3-[3-(4,5-diphenyloxazol-2-yl)-3-cyclohexen-1-yl]benzoate

IR (film) : 2931, 1718, 1537, 1444, 1286, 1196, 1109, 964, 756, 694 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.2 (3H, m), 2.42-3.16 (4H, m), 3.92 (3H, s), 6.89 (0.4H, br s), 6.97 (0.6H, br s), 7.25-7.53 (8H, m), 7.53-7.73 (4H, m), 7.88-8.02

(2H, m)

Mass (m/z) : 436 $(M+H)^+$

(3) Methyl 3-{1-[(4,5-diphenyloxazol-2-yl)methyl]-2-cyclohexen-2-yl}benzoate

IR (film) : 2933, 1726, 1720, 1579, 1442, 1292, 1227, 1110, 1061, 964, 762, 696 cm^{-1}

NMR ($CDCl_3$, δ) : 1.67-1.82 (2H, m), 1.84-1.95 (2H, m), 2.20-2.40 (2H, m), 2.79 (1H, dd, J=8.5, 14.7Hz), 2.92 (1H, dd, J=6.2, 14.7Hz), 3.40-3.53 (1H, m), 3.81 (3H, s), 6.03 (1H, dt, J=0.7, 3.2Hz), 7.21-7.40 (7H, m), 7.42-7.56 (4H, m), 7.80 (1H, d, J=7.4Hz),8.00 (1H, d, J=1.7Hz)

Mass (m/z) : 450 $(M+H)^+$

Example 59

The following compounds described in (1) to (3) were prepared in a similar manner to that of Example 24.

(1) A mixture of 3-{[3-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl}benzoic acid and 3-{[3-(4,5-diphenyloxazol-2-yl)-3-cyclohexen-1-yl]methyl}benzoic acid

IR (KBr) : 3432, 2924, 1695, 1535, 1446, 1298, 1211, 1074, 964, 764, 692 cm^{-1}

NMR ($CDCl_3$, δ) : 1.3-1.5 (1H, m), 1.5-2.4 (4H, m), 2.5-2.9 (4H, m), 6.79 (0.4H, br s), 6.88 (0.6H, br s), 7.3-7.7 (12H, m), 7.9-8.0 (2H, m)

Mass (m/z) : 436 $(M+H)^+$

(2) A mixture of 3-[3-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]benzoic acid and 3-[3-(4,5-diphenyloxazol-2-yl)-3-cyclohexen-1-yl]benzoic acid.

IR (film) : 3435, 2927, 1693, 1446, 1292, 1076, 966, 764, 694 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.2 (3H, m) 2.4-3.18 (4H, m), 6.90 (0.4H, br s), 6.97 (0.6H, br s), 7.3-7.74 (12H, m), 7.90-8.06 (2H, m)

Mass (m/z) : 422 $(M+H)^+$

(3) 3-{1-[(4,5-Diphenyloxazol-2-yl)methyl]-2-cyclohexen-2-yl}benzoic acid

IR (KBr) : 3448, 2925, 1709, 1444, 1282, 1224, 1063, 760, 694 cm^{-1}

NMR ($CDCl_3$, δ) : 1.56-1.90 (4H, m), 2.12-2.27 (2H, m), 2.78 (2H, d, J=6.5Hz), 3.3-3.46 (7H, m), 6.04 (1H, t, J=3.3Hz), 7.3-7.6 (12H, m), 7.73 (1H, d, J=7.7Hz), 7.92 (1H, s), 12.9 (1H, br s)

Mass (m/z) : 436 $(M+H)^+$

Example 60

The following compounds described in (1) to (5) were obtained in a similar manner to those of Example 22 and Example 24.

(1) 4-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclohepten-1-yl]-methyl}benzoic acid

NMR ($CDCl_3$, δ) : 1.4-2.0 (6H, m), 2.3-2.6 (2H, m), 2.98 (1H, m), 3.05 (1H, m), 3.82 (1H, m), 7.09 (1H, t, J=8.0Hz), 7.2-8.2 (14H, m)

Mass (m/z) : 450 $(M+H)^+$

(2) 4-{[3-(4,5-Diphenyloxazol-2-yl)bicyclo[2.2.1]hept-2-en-2-yl]methyl}benzoic acid

IR (Nujol) : 1700 cm^{-1}

NMR ($CDCl_3$, δ) : 1.0-2.0 (6H, m), 2.82 (1H, br s), 3.62 (1H, br s), 3.70 (1H, d, J=14Hz), 4.40 (1H, d, J=14Hz), 7.2-8.1 (14H, m)

Mass (m/z) : 448 $(M+H)^+$

(3) 3-{[2-(4,5-Diphenyloxazol-2-yl)-2-cycloocten-1-yl]-methyl}benzoic acid
Mass (m/z) : 464 $(M+H)^+$

(4) 4-{[2-(4,5-Diphenyloxazol-2-yl)-2-cyclopenten-1-yl]-methyl}benzoic acid
IR (Nujol) : 1680 cm^{-1}
NMR ($CDCl_3$, δ) : 1.8-2.2 (2H, m), 2.3-2.5 (2H, m), 2.72 (1H, dd, J=9, 14Hz), 2.99 (2H, m), 3.48 (1H, dd, J=5, 15Hz), 3.60 (1H, m), 6.71 (1H, m), 7.2-8.1 (14H, m)
Mass (m/z) : 422 $(M+H)^+$

(5) 3-{{2-[4,5-Di(4-methylphenyl)oxazol-2-yl]-2-cyclohexen-1-yl}methyl}benzoic acid
IR (Nujol) : 1680 cm^{-1}
NMR ($CDCl_3$, δ) : 1.5-2.4 (6H, m), 2.33 (6H, s), 2.60 (1H, m), 3.1-3.4 (2H, m), 6.90 (1H, m), 7.0-8.2 (14H, m)
Mass (m/z) : 464 $(M+H)^+$

(6) 3-{[2-(4,5-Diphenylthiazol-2-yl)-2-cyclohexen-1-yl]-methyl}benzoic acid
IR (Nujol) : 1680 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-2.8 (7H, m), 3.2-3.4 (2H, m), 6.64 (1H, m), 7.2-8.2 (14H, m)
Mass (m/z) : 452 $(M+H)^+$

Example 61

The following compounds described in (1) to (2) were obtained according to a similar manner to that of Example 29.

(1) 4-{[3-(4,5-Diphenyloxazol-2-yl)bicyclo[2.2.1]heptan-2-yl]methyl}benzoic acid
Mass (m/z) : 450 $(M^++H)^+$

(2) 4-{[2-(4,5-Diphenyloxazol-2-yl)-1-cyclopentyl]methyl}-benzoic acid

IR (Nujol) : 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.5-2.9 (9H, m), 3.48 (1H, m), 7.2-8.0 (14H, m)

Mass (m/z) : 423 $(M+H)^+$

Industrial Applicability

Prostaglandin E_2 receptor blockers, particularly EP_4 receptor blocker, have diuretic activity with a various characteristics such as a lower kaluretic activity relative to natriuretic effect, a larger phosphorus excretion, or the like. Therefore, They are useful for preparation of medicament indicated treating or preventing various edema, hypertension, premenstrual tension, urinary calculus, oliguria, hyperphosphaturia, or the like.

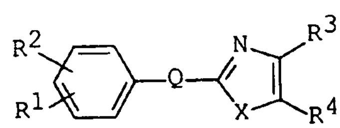
CLAIMS

1. A use of the PGE_2 receptor blocker for the manufacture of a medicament having a diuretic activity.

2. A use of the PGE_2 receptor blocker for the manufacture of a medicament for treating or preventing various edema, hypertention, premenstrual tension, urinary calculus or oliguria.

3. A use according to claim 1 or 2, wherein PGE_2 receptor blocker is EP4 receptor blocker.

4. A use according to claim 1 or 2, wherein PGE_2 receptor blocker is a compound of the formula :



(I)

wherein

R^1 is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; hydroxy; halo(lower)alkylsulfonyloxy; lower alkoxy optionally substituted with hydroxy or carbamoyl; aryl substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,

R^2 is hydrogen or lower alkyl,

R^3 is aryl optionally substituted with halogen,

R^4 is aryl optionally substituted with halogen,

Q is $-A^1-\underset{A^2}{\bigcirc}-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene, $\underset{A^2}{\bigcirc}$ is cyclo(C_5-C_9)alkene,

cyclo(C_3-C_9)alkane, bicyclo(C_6-C_9)alkene or bicyclo(C_5-C_9)alkane, and $-A^3-$ is a single bond or lower alkylene], and

X is O, NH or S,

or its salt, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

5. A use according to the claim 4, wherein X is O.

6. A use according to the claim 5, wherein

R^1 is lower alkyl substituted with carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; lower alkoxy substituted with carbamoyl; aryl substituted with carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with lower alkylsulfonyl.

7. A use according to the claim 6, wherein

R^1 is lower alkyl substituted with carboxy; carboxy; carbamoyl; tetrazolyl; lower alkoxy substituted with carbamoyl; aryl substituted with carboxy or carbamoyl, and

Q is $-A^1-\underset{A^2}{\bigcirc}-A^3-$ [in which $-A^1-$ is methylene, $\underset{A^2}{\bigcirc}$ is cyclo(C_5-C_7)alkene, cyclo(C_5-C_7)alkane, bicyclo[2.2.1]heptene or bicyclo[2.2.1]heptane, and $-A^3-$ is a single bond].

9. A method for treating or preventing various edema, hypertention, premenstrual tension, urinary calculus or oliguria which comprises administering an effective amount of the PGE_2 receptor blocker to human beings or animals.

10. The method for treating or preventing inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, allergic disease, cancer or neurodegenerative diseases which comprises administering an effective amount of the PGE_2 receptor blocker of claim 6 to human beings or animals.

11. A use of the PGE_2 receptor blocker for the manufacture of a medicament for treating or preventing various edema, hypertention, premenstrual tension, urinary calculus or oliguria in human beings or animals.